

SEASONAL VARIATION IN TUBERCULOSIS

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SEASONAL VARIATION IN TUBERCULOSIS

INTRODUCTION

Some of the oldest problems in biology have been strangely neglected in the rapid advancement of scientific knowledge. One of these concerns seasonal variation in man. It is probably 50,000 years ago since man first became accustomed to organising means of countering seasonal difficulties, but even yet the essential nature of the problem he was striving with remains unsolved. Indeed it is only within comparatively recent times that the subtlety of the issues involved has been appreciated.

The first deliberate attempts which historians have recorded on the part of man to overcome seasonal embarrassments, refer merely to the storage of food and fuel during the summer for consumption during the winter. The "squatting places" of Neanderthal man, usually caves near streams, contain abundant evidence of this kind of activity.

Long after Neanderthal man had become an extinct/

extinct race, Primordial man treated seasonal changes quite differently. He could not "squat" all winter since he was unable to store enough food for his sheep and cattle. So he and his beasts wandered southward in winter to warm lands where they need have no fear of snow and frost, and northward again in summer to more temperate regions where pastures would not become scorched under a burning sun.

About 10,000 years ago Neolithic man made the greatest advance up to that time in the history of the world, by evolving a method of agriculture. In doing so he found that he could time the changing seasons not only by the sun, but by the stars as well. He ultimately preferred to till his land and sow his seed by the stars, and in tilling, sowing and reaping he laid the foundations of civilisation.

But as civilisation became more complicated disease began to make its appearance. Man found that he must study the seasons anew, though not as they affected his sowing and reaping, but as they affected himself, for he began to observe that health and sickness frequently alternated in a definite seasonal way. Here was a strange problem, and a strange problem it remains.

It is not possible to state with certainty which diseases first attracted attention on account of their seasonal incidence, but it is safe to assume that/

that they were the acute respiratory infections which occur with such regularity in the middle of winter. Some time later it is probable that what are now known as the zymotic diseases furnished the information that winter is not the only danger period; that even in the height of summer the time might be appropriate for the occurrence of certain types of sickness.

Gradually, for knowledge of these things gathers not in an hour but in the flight of years, seasonal change was found to occur in a wide variety of other ailments, for example, in eclampsia and the toxæmias of pregnancy; in syphilis and lupus; in gastric ulcer, and even in the acidity of the gastric juice in normal people. This last type of variation, that in normal persons, has given rise to the latest development in the study of a wide question, and information is gradually accumulating on seasonal trends in human and animal physiology.

Seasonal variation in health and disease represents a problem which will ultimately be explained by the biologist. Meantime the physician who remembers that he ought to be a biologist, will do well to make such observations on the subject as his daily contact with men and disease will allow. The object of the following work is to record the writer's own investigations on seasonal change, as noted in tuberculosis and other diseases, and to advance as far as/

as possible in the light of present knowledge, an explanation as to the cause of these phenomena.

The present work falls conveniently into four parts.-

- I Seasonal Variation in Tuberculous Lesions.
- II Seasonal Variation in Systemic Disturbance.
- III A Statistical Inquiry into Seasonal Variation in Mortality.
- IV Discussion.

Methods of Study.- Apart from inquiries based solely on vital statistics, which form Part III of this work, two methods of investigating seasonal variation in disease may be noted. In the first place it is possible to select some incident in the course of a disease, (e.g. haemoptysis in pulmonary tuberculosis) and to ascertain if, in a large series of cases, this particular event exhibits a seasonal tendency. Secondly, it is possible to select a group of cases, to observe them continuously for a complete year, and to ascertain if any of the regularly recorded changes (e.g. body weight) exhibits seasonal variation. Both methods were employed in this work, the former more especially in Part I (on local lesions) and the latter in Part II (on the systemic factor).

The local lesions studied were those occurring in lymphatic tuberculosis and pulmonary tuberculosis.

In lymphatic tuberculosis, consideration was given to glandular enlargement, and to the subsequent development of pus formation. In pulmonary tuberculosis the amount of sputum expectorated, and the incidence of haemoptyses were investigated.

The manifestations of the systemic factor in tuberculosis which attracted attention were the body temperature, the pulse rate, the body weight, and the reaction to tuberculin.

Acknowledgements.- The writer is doubly indebted to Professor Sir Robert Philip who as Honorary Medical Director of Southfield Sanatorium Colony, Edinburgh allowed him to analyse the case records of that institution; and who as Curator of the Laboratory of the Royal College of Physicians of Edinburgh placed at his disposal sufficient tuberculin to continue an investigation for three years. He is also indebted to Dr A. Fergus Hewat for permission to analyse the records of the Tuberculosis Department of the Royal Infirmary, Edinburgh: to Lieut. Colonel McKendrick, Superintendent of the Laboratory of the Royal College of Physicians, Edinburgh for advice regarding the presentation of the results of the investigation of the seasonal change in the sputum in pulmonary tuberculosis: to Dr Peter L. McKinlay of the Department of Health for Scotland for advice on the presentation of certain data in Part III of this work, and to/

to Dr A.C. Aitken of the Statistical Department of Edinburgh University who taught the writer the application of the "Chi-squared Test" on certain of the results involved: to Mr A. Gofton, F.R.C.V.S., Chief Veterinary Inspector of the City of Edinburgh, for permission to analyse the records of his department in the investigation on seasonal variation of tuberculosis in cattle*: and last but not least to the late Dr D.G.S. McLachlan for much helpful criticism and advice, frequently asked and always readily given.

Christopher Clayson.

Edinburgh 1936.

* This investigation was only made possible after the remainder of the work had been completed, and in consequence it was necessary to incorporate it in an additional appendix.

PART I

SEASONAL VARIATION IN TUBERCULOUS LESIONS.

On theoretical grounds it may be supposed that if tuberculosis is one of the morbid conditions which are affected by seasonal influences then all manifestations of the disease will present evidence of seasonal change. In practice, however, it is not possible to observe this process in all tuberculous lesions for seasonal change is readily detectable only in those forms of tuberculosis which provide visible indications of activity.

Thus Vieil (1928) found that in Lupus, exacerbations were most frequent in February and the first half of March, whilst the greatest improvement occurred in August and September. He concluded that the conditions of life for the tubercle bacillus were most favourable in the spring.

Other skin lesions related to tuberculosis have also attracted attention, and Levin (quoted by St. Engel and Pirquet, 1930) described a remarkable seasonal curve in the incidence of cases of Erythema Nodosum. He found that the largest proportion of cases came under observation in April and May, whilst those who reported their condition during August, /

August, September and October formed a relatively small fraction of the series.

In relation to thoracic tuberculosis, pleurisy and haemoptysis have been stated to present a seasonal incidence. Brinkmann in an address to the German Society of Tuberculosis Physicians in 1928 described a spring time peak in the occurrence of both these manifestations of tuberculosis. The available abstract of this paper is however lacking in detail, but further investigations by Anders (1907,1909), Burns (1922), Redeker (1931), Bratt and Ingebrigtsen (1932), as well as by the present writer will receive attention later in this work.

Stephani and Trouard-Riolle (1929) have investigated seasonal variation in the blood with particular reference to the Arneth count, a valuable mirror of local change, in patients suffering from pulmonary tuberculosis. These authors stated that they observed a characteristic "shift to the left" in the spring in 84 out of 98 cases, and that a less marked autumnal deviation (also to the left) occurred in 38 out of 59 cases. Two possible defects tend to detract from this interesting observation. Firstly the authors do not define their conception of "une déviation a gauche caractéristique", nor do they give a summary of their readings in any more than one of the 84 cases in whom this phenomenon is stated to/

to have occurred. Secondly no information is given on the important question as to what proportion of these cases presented other evidence of activity during the critical period, and in what proportion the observation on the blood constituted the only indication of seasonal change.

The writer has endeavoured to supplement the above observations by inquiring into the effects of seasonal influence as encountered in glandular and pulmonary lesions. In the former manifestation two events were selected for examination, namely, the appearance of glandular enlargement and the formation of pus in those cases in which the process was palpable either in cervical or axillary regions. In pulmonary tuberculosis the signs to which attention was devoted were the amount of sputum and the incidence of haemoptyses.

SEASONAL INCIDENCE IN THE APPEARANCE OF GLANDULAR ENLARGEMENT IN LYMPHATIC TUBERCULOSIS.

Introduction.— The object of the following enquiry is to ascertain if any seasonal incidence in the onset of glandular swelling is apparent from a study of the case records of a large number of/

of patients suffering from tuberculosis of the lymphatic system. The sources of the clinical material upon which the investigation is based were the Tuberculosis Department of the Royal Infirmary of Edinburgh, and Southfield Sanatorium Colony, Edinburgh.

Selection of Cases.- It was not possible to include every case of glandular tuberculosis in the files of the institutions named above in the present series of patients, since many were unable to recall even approximately the date on which the condition first attracted attention. Whilst the majority of cases reported the onset of the glandular enlargement to their medical advisers very soon after the process became apparent, a considerable proportion only sought guidance after the swelling had persisted for many months, and consequently they could not remember when it first began.

It was necessary, therefore, in attempting to determine with reasonable precision the date of onset of the patient's condition to adopt some rule by which it was possible on the one hand to accept the data given by the patient concerning the early stages of his illness as being correct, or on the other hand to reject them as being probably inaccurate. With this aim in view many patients were questioned in an endeavour to assess the value of their memories in regard to previous events. It appeared that patients, for the most part answered without hesitation/

hesitation questions concerning the commencement of the initial glandular swelling, if the morbid process had appeared within three months of the inquiry being put to them, though some doubt frequently existed on the point where a greater interval than this had elapsed. In order to eliminate this element of doubt, therefore, no case was incorporated in this investigation who delayed for more than three months in seeking medical guidance.

The adoption of this rule for selecting cases resulted in the discarding of a large proportion of the available material, but as a result the conclusions arrived at may be advanced the more confidently since the patient who seeks advice early is the careful patient to whose word due weight may be given.

In this way it was possible to determine accurately the date of the appearance of glandular enlargement in 399 cases of lymphatic tuberculosis. In none of these patients was the duration of the disease more than three months.

Recurrences.- The scrutiny of the case records of patients suffering from glandular tuberculosis revealed the fact that in a proportion of cases the enlargement of the glands was a reactivation of a tuberculous process which had been latent for a period of time varying from two to nearly twenty years. There is no apparent reason why such relapses should present a seasonal reaction in any way different from that/

that observable in the initial activation of the tuberculous process, and indeed evidence will shortly be advanced to show that no such differences occur. Meanwhile it may be stated that in the series of cases which form the subject of the present study there were 42 patients who presented recurrences of glandular tuberculosis of not more than three months' duration. In all therefore the date of glandular enlargement was known in 441 cases of tuberculosis of the lymphatic system.

Classification and Results.- The above series of cases was now classified according to the month of year in which the glandular enlargement was noted to have commenced. The results are presented graphically in Figure 1 and numerically in Table 1.

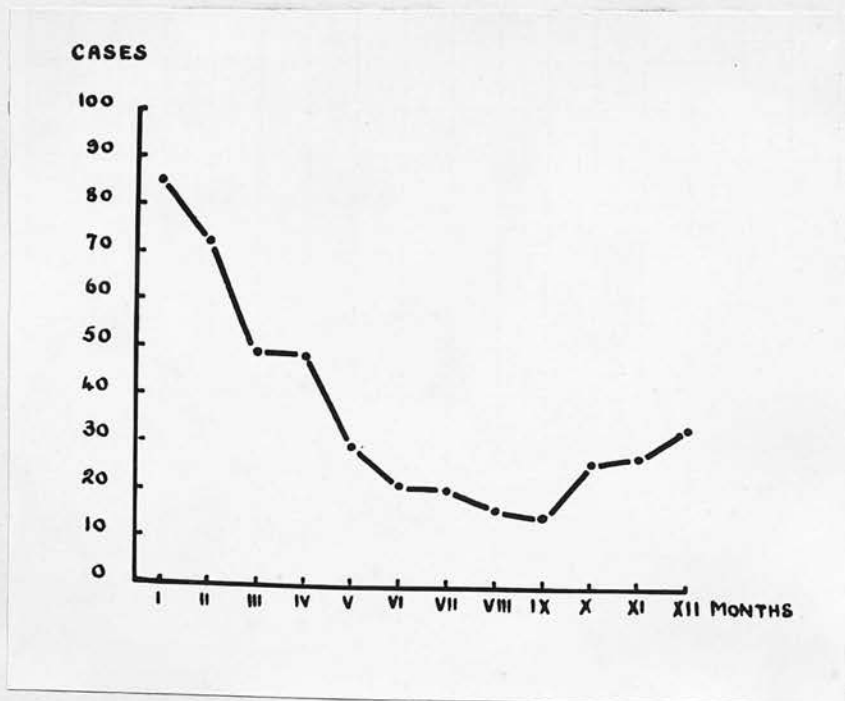


Figure 1.- Seasonal incidence in the appearance of glandular swelling in 441 cases of lymphatic tuberculosis.

The general trend of the seasonal tendency involved may be readily observed on reference to Figure 1, in which the ordinate represents the number of cases and the abscissa the time of year. The peak point representing the maximum frequency of glandular swelling occurred in January and was followed by a rapid diminution in the number of cases during the spring months. From the month of May onwards relatively fewer cases were observed, the minimum number being registered in August and September. A gradual increase in the number of cases was noted during the last three months of the year. A more detailed analysis may be seen in Table 1.

Table 1.- Classification of 441 cases of lymphatic tuberculosis according to the month of year in which glandular enlargement was first observed.

Month	Number of cases	Percentage number of cases
I	85	19.3
II	72	16.3
III	49	11.1
IV	48	10.9
V	29	6.6
VI	21	4.8
VII	20	4.5
VIII	16	3.6
IX	15	3.4
X	26	5.9
XI	27	6.1
XII	33	7.5

From the above Table it may be noted that of 441/

441 cases, as many as 157 or 35.6 per cent. were shown to be the subjects of glandular enlargement during the months of January and February, whilst 254 cases or 57.6 per cent. were recorded during the first four months of the year. On the other hand it will also be observed that during the months of August and September only 51 cases were registered or 7.0 per cent. of the total, whilst relative increase in the number of cases occurred during the last quarter of the year.

Conclusion.- Glandular enlargement in patients suffering from tuberculosis of the lymphatic system occurs more commonly during January and February, and less commonly during August and September than at other times of year.

THE SEASONAL INCIDENCE OF PUS FORMATION IN GLANDULAR TUBERCULOSIS.

Introduction.- The second part of this study deals with the relationship of the seasons to the formation of pus in tuberculous glands. The aim of the investigation was to determine at what time of year, if any, that activity of the tuberculous process was most likely to determine the change from caseation to liquefaction. It is well known that caseation may never proceed to liquefaction, or that/

that if it does so, it may take any length of time. The causes of this change are still the subject of much discussion, but that the season of the year may be of some importance is a possibility which is investigated in the following pages. The writer's findings up to 1931 were published in 1932 in co-authorship with Dr J.C. Simpson, Southfield Sanatorium Colony, who first suggested a possible seasonal occurrence of pus formation in tuberculous glands.

Selection of Cases.- The sources of the material on which the present study was based were the same as indicated in the last section.

Throughout the series, the case records of patients suffering from glandular tuberculosis were examined for notes relative to the formation of pus in the glands, and the date was recorded on which the evacuation of pus was performed. In a few additional patients the glandular abscess had burst before aspiration was possible, and where this was so the date on which the abscess had burst was recorded. All patients in whose history there existed some element of doubt were excluded from the series. There were many, for example, who presented a history of glandular swelling, followed by operation, since when there had been a continual discharge from the wound. Such cases were not accepted on the ground that the discharge might have been provoked by an infection of the wound from without. Likewise, patients in whom/

whom the affected glands showed softening but did not actually fluctuate enough to render the evacuation of pus possible, were also excluded.

It should be explained here, lest some confusion arise, that not all the cases which figure in the present series were included in the previous group which dealt with the earlier manifestations of simple glandular enlargement. Naturally not all the patients in the former group showed subsequent abscess formation, and on the other hand there were some, concerning whom definite evidence regarding the removal of pus was forthcoming, who had no knowledge as to when the disease first made its appearance. Only to a limited extent, therefore, did the two groups overlap.

Initial Change from Caseation to Pus Formation.-

Out of the series of records examined it was found that accurate information could be obtained regarding the date of formation of pus in 246 patients. These were classified into twelve groups according to the month of the year in which pus was evacuated. The results were recorded in graphic form in Figure 2 (page 17). It should be observed that the aspiration of pus from enlarged glands was performed in 17 cases during the month of January. In February the number increased whilst in March a peak was recorded (57 cases) indicating a much more frequent occurrence of pus formation during that month than at any other time of year. A rapid diminution in the number of/

of cases ensued, and it was found that the removal of pus was relatively seldom required during August, September and October.

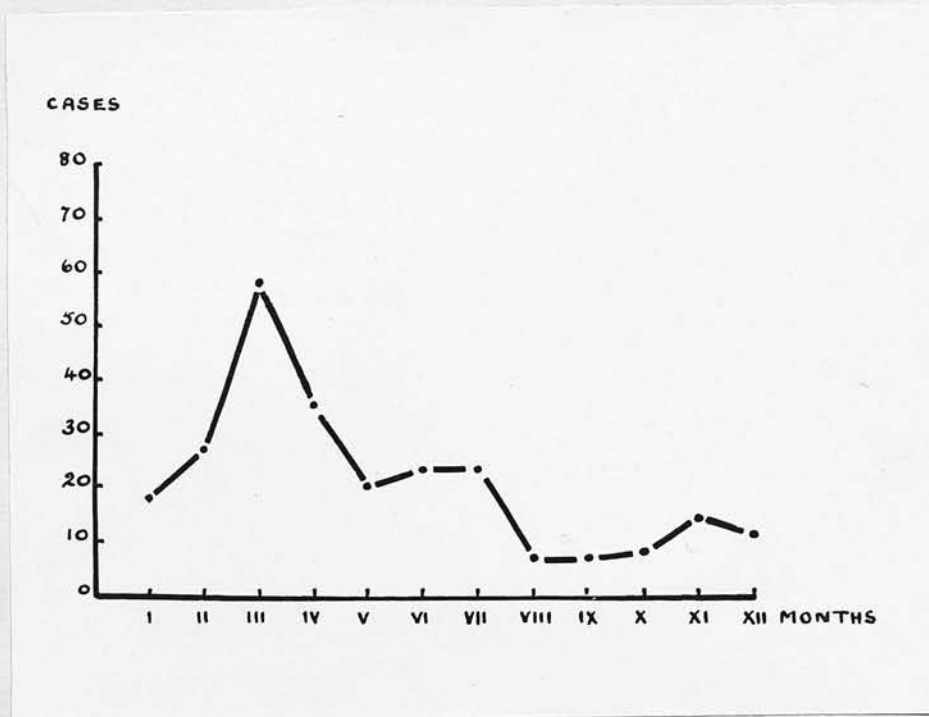


Figure 2.- Seasonal incidence in the formation of pus in 246 cases of glandular tuberculosis.

Recurrences of Pus Formation.- Some reference has already been made to the fact that exacerbations in glandular tuberculosis tend to show similar seasonal changes as do the lesions at the onset of the disease. It is now proposed to present the histories of certain illustrative cases in whom recurrences were observed from time to time, and to discuss this statement a little more fully.

Case 1, J.R., aet.14.- This patient had suffered from enlarged cervical glands on the right side for/

for ten years when he came under observation in July, 1920. The last exacerbation which caused him to seek advice attracted attention in June, 1920. In MARCH, 1921, after a period of improvement, the glands in the left side of the neck began to swell and were aspirated in APRIL. Once again the patient improved steadily but in FEBRUARY, 1922 the glands again became swollen and required immediate aspiration.

Case 2, A.F., aet.42.- The right cervical glands became enlarged in 1918 but an exacerbation early in 1920 led to their removal in MARCH of that year. Thereafter progress was satisfactory until JANUARY, 1923 when the right axillary group of glands became involved, and were removed the following APRIL. After this operation the patient improved steadily until JANUARY, 1924. At this time the right cervical glands enlarged again, softened in FEBRUARY and were aspirated. Once again improvement occurred and was maintained until JANUARY, 1925, when the glands enlarged rapidly, softened in MARCH, and were aspirated. Since then no recurrence has been noted up to the present time.

Case 3, M.M'J., aet.36.- This patient had suffered from enlarged cervical glands in childhood, but these disappeared and caused no further trouble till 1929. In JANUARY of that year the glands on the right side of the neck became swollen, but the swelling gradually disappeared during the summer. The/

The same sequence of events began again in FEBRUARY, 1930. In JANUARY, 1931 the glands again enlarged. This time they softened, and were aspirated in MARCH. A period of quiescence ensued, but in JANUARY, 1932 marked glandular enlargement required attention, and pus was evacuated in the month of APRIL after which the swelling subsided.

Case 4, N.M., aet. 30.- In the spring of 1915 the left cervical glands became enlarged. The swelling disappeared, however, and attracted no further notice till FEBRUARY, 1918, when the submental glands began to swell. A period of quiescence ensued until MARCH, 1919 when the submental glands increased markedly in size. From 1919 to 1922 there was no disturbance but in FEBRUARY, 1922 there was much swelling and systemic upset. This improved but in APRIL, 1923 there was a recurrence which was so severe that the patient ceased work. After recovering from this there followed a period of retrogression until FEBRUARY, 1929. At this time the right cervical and posterior auricular glands became swollen, and were aspirated. In MARCH, 1930, the same glands enlarged again and were aspirated. A further period of quiescence ensued until MARCH, 1931, when the right supraclavicular glands became swollen, and the right cervical glands enlarged and pus was evacuated.

A consideration of the data furnished by the/

the histories of these cases in which the process was intermittently active for a number of years, emphasises the seasonal tendency to pus formation, and it is unnecessary to review in detail the histories of all the 34 patients who presented similar features, and in whom pus was aspirated on 78 occasions. In many the second period of pus formation occurred exactly a year after the first, whilst in the interval a period of improvement had taken place. In classifying the results it was not considered that a temporary cessation of pus formation, followed by a recurrence in a month or two, constituted evidence of seasonal change. But in those cases in which the lesion had apparently become quiescent, and where there had been no evidence of active disease for a period of six months, a renewal of activity at the end of that time was regarded as a true exacerbation of the disease, and the season of the year was then noted.

The formation of pus in this group of cases in each calendar month of the year is recorded in Figure 3 (page 21). A similar form was noted to that described in Figure 2, where 246 cases were considered and no attention paid to reactivations. For the most part pus formation was observed in February, March and April, with a peak in March, but it was relatively uncommon in the autumn. The indication is, therefore, that whatever seasonal change occurs /

occurs in glandular tuberculosis, the factors controlling it govern relapses as well the initial activation.

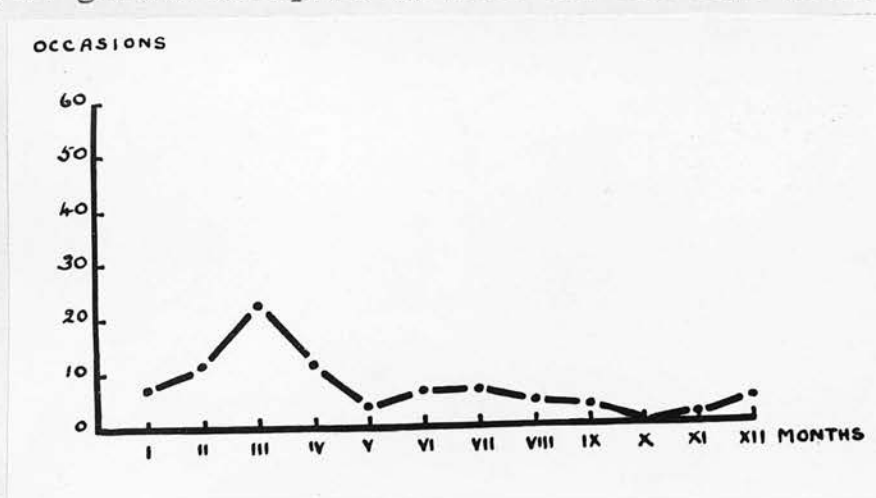


Figure 3.-Monthly distribution of occasions (78) on which pus formation was observed in 34 patients who were the subjects of recurrences.

Summary of All Cases.- When all the occasions are considered on which pus formation was observed, namely once in 246 patients, twice in 34 patients, and three times in 5 patients, the total number of activations is found to be 290. The curve representing the seasonal trend on these occasions is depicted in Figure 4.

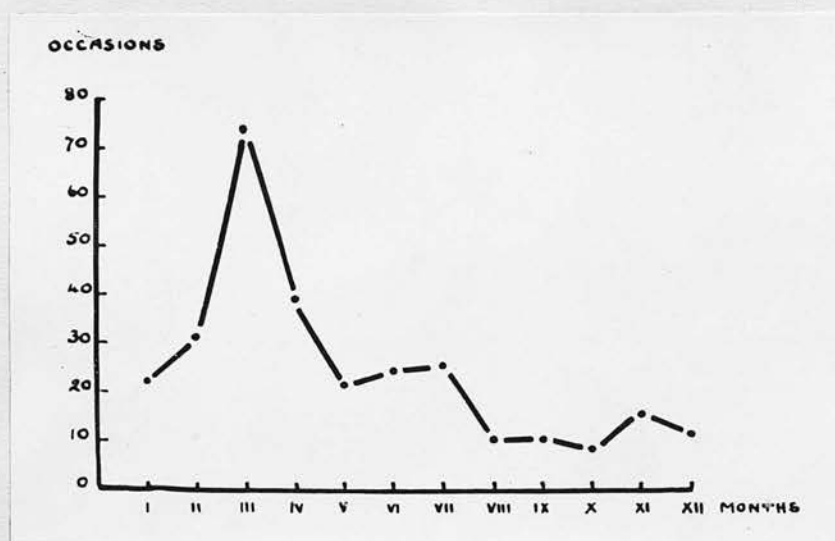


Figure 4.- Monthly distribution of the total number of occasions (290) on which pus formation was observed in 246 cases of glandular tuberculosis.

Reference to Figure 4 indicates that a marked seasonal trend is observable in the formation of pus in glandular tuberculosis. A sharp rise from the beginning of the year to a pronounced peak in the month of March shows how commonly aspiration was required at that time. During April the evacuation of pus, although practised much less frequently than in March, was required much more frequently than during the remainder of the year. Indeed pus formation was relatively uncommon during August, September and October.

Table 2 furnishes a precise analysis of the above data. During March and April 113 aspirations of pus,

Table 2.- Classification of 290 occasions on which pus formation occurred in 246 patients suffering from glandular tuberculosis, according to the month when aspiration was performed.

Month	Number of occasions on which aspiration of pus was performed	
	absolute	per cent.
I	22	7.6
II	31	10.7
III	74	25.6
IV	39	13.4
V	21	7.2
VI	24	8.3
VII	25	8.6
VIII	10	3.4
IX	10	3.4
X	8	2.8
XI	15	5.2
XII	11	3.8

or 39 per cent. of the total, were performed. Conversely, during the period of three months from August to October evacuation of pus was only required on 28 occasions or 9.6 per cent. of the total.

Conclusion.- Pus formation in glandular tuberculosis is relatively common during March (and April) indicating a greater liability for caseation to lead to liquefaction at that time, whilst during August, September and October this change is more unusual.

SEASONAL VARIATION IN PULMONARY TUBERCULOSIS

The determination of possible seasonal trends in pulmonary tuberculosis is not so simple as it is in glandular lesions. This is no method of observing the initial changes in the lung comparable to the palpation of swollen glands. Redeker (1931) endeavoured to express the seasonal change observable in the occurrence of symptoms of pulmonary tuberculosis in adolescents, and found that the initial complaints arising from the disease, or from reactivations of the disease, were noticed with maximum frequency in May and/

and June. He argued that the pathological changes in the lung required from four weeks to several months to give rise to symptoms of disease, and therefore the onset of pulmonary tuberculosis could be stated to occur most frequently in March and April.

The seasonal variation observable in the occurrence of pleurisy with effusion may also be mentioned in connection with pulmonary tuberculosis. Out of the 24 cases observed by the writer 12 were diagnosed in the months of March and April. In all cases the diagnosis was confirmed by exploratory puncture. This is a small number of cases, for pleurisy with effusion is not such a common feature of sanatorium work as is generally supposed. But a much larger series of cases was collected by Bratt and Ingebrigtsen between 1918 and 1929 (1932). These authors described a marked seasonal incidence in pleurisy with effusion. Of 388 cases 15.3 per cent. were noted to occur in March. This was a much larger proportion than in any other month, though a secondary peak in the incidence of the disease was observable in December and January.

In the present work special attention was devoted to investigating possible seasonal trends in the abundance of expectoration, or in the incidence of haemoptyses in patients suffering from pulmonary tuberculosis.

SEASONAL VARIATION IN THE PRODUCTION OF SPUTUM

Introduction.- In pulmonary tuberculosis the production of sputum in the counterpart of the formation of pus in glandular tuberculosis.

It was natural, therefore, to endeavour to determine whether the seasonal relationship which was observable in the lymphatic system, was also demonstrable in pulmonary lesions.

Two avenues of investigation suggested themselves. Firstly, the bacillary content of the sputum could be estimated with a view to ascertaining if the numbers of tubercle bacilli present varied at different times of year. Secondly, the volume of sputum could be measured, and a parallel observation conducted concerning the abundance of expectoration at different times of year.

Neither of these methods was devoid of difficulty. The mathematical enumeration of tubercle bacilli in sputum is not a simple matter, and the designations which usually suffice for clinical records (namely -, +, ++, +++) were totally insufficient for a more accurate estimation of the number of bacilli present. Even the detailed method by which Gaffky defined twelve numerical standards for the purpose was considered to be inadequate.

For an experimental period the following method was adopted in ten patients. Films of sputum were/

were made each week, as far as possible of uniform thickness, and stained by the Ziehl-Neelsen method. The number of bacilli present in thirty consecutive fields of the microscope were counted, and an average per field calculated. No great uniformity in the weekly figures was expected, but nevertheless the writer did not anticipate the remarkable variation which occurred from week to week. It was considered that the figures gained afforded a very doubtful indication of the numbers of bacilli actually present in the sputum, and that no interpretation could be made regarding the relationship of seasonal influence to the variable numbers of bacilli recorded. The method was therefore abandoned.

The second method of investigating a possible connection between the production of sputum in pulmonary tuberculosis and the season of the year, was to measure the volume of the expectoration. It was hoped that the past records of Southfield Sanatorium Colony would contain ample data wherewith to formulate a conclusion on the subject. But the amount of sputum varied so widely that the existing measurements which (in line with the common sanatorium practice) had been made twice a week, could not provide sufficiently accurate figures on which to base any deductions. A more reliable method was therefore devised.

Method of Measuring Sputum.-- The following/

following method was adopted in 1932 and has become a routine practice. The contents of each patient's sputum flask (or flasks) were emptied every morning into tall, narrow measuring flasks of 100 cc. capacity. The contents were allowed to settle for five minutes during which time the sputum sank to the bottom, and the saliva and froth rose to the top. When the sputum had separated out the amount could be determined with ease and accuracy. All recordings were made in cubic-centimetres. The accumulated data were thus based on the entire amount of expectoration in each individual and not on samples.

Results.- From the inception of the above method until June 1935 it was possible to measure the expectoration in 31 cases daily for at least one year, and in certain instances for more than that period. It is not proposed to preface the results by inserting at the present juncture a detailed description of all these cases, though six illustrative examples may be seen on reference to Figures 5 and 6. All the relevant facts may be consulted in Appendix I (page 214), which contains the monthly figures and brief descriptions of all cases, together with evidence indicating that the curves described are seasonal and not due to special methods of treatment.

The series of curves in Figure 5 are illustrative of three patients who were in residence at Southfield Sanatorium Colony for one year from/

from January to December. The curves in these Figures represent the average daily output of expectoration for each month of the year. It will be seen that the

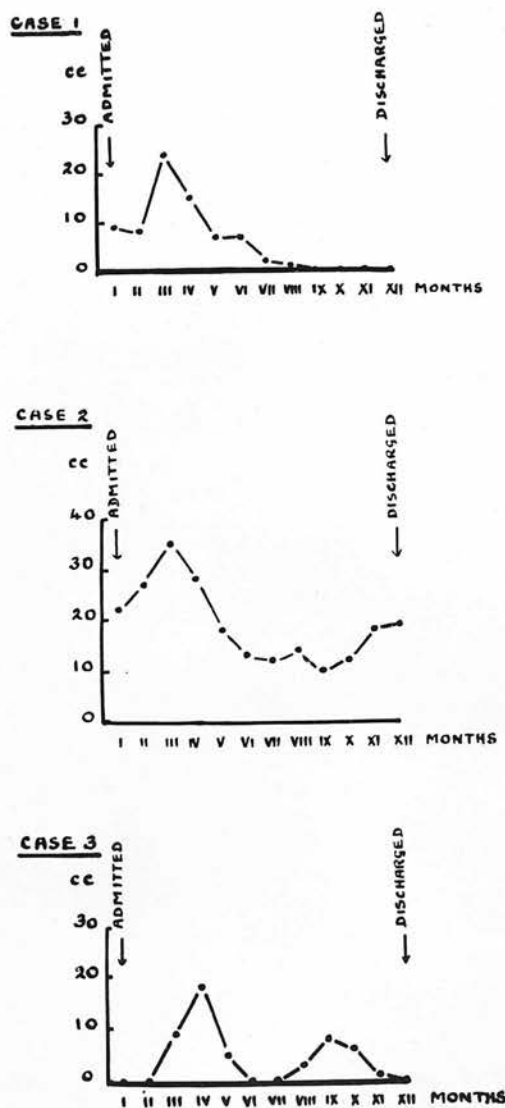


Figure 5.- The average daily volume of expectoration for each month of a complete year in three illustrative cases. (Details in Appendix I.)

sputum was most abundant in these patients during the/

the spring. In cases 1 and 2 the maximum amount was registered in March and in case 3 in April.

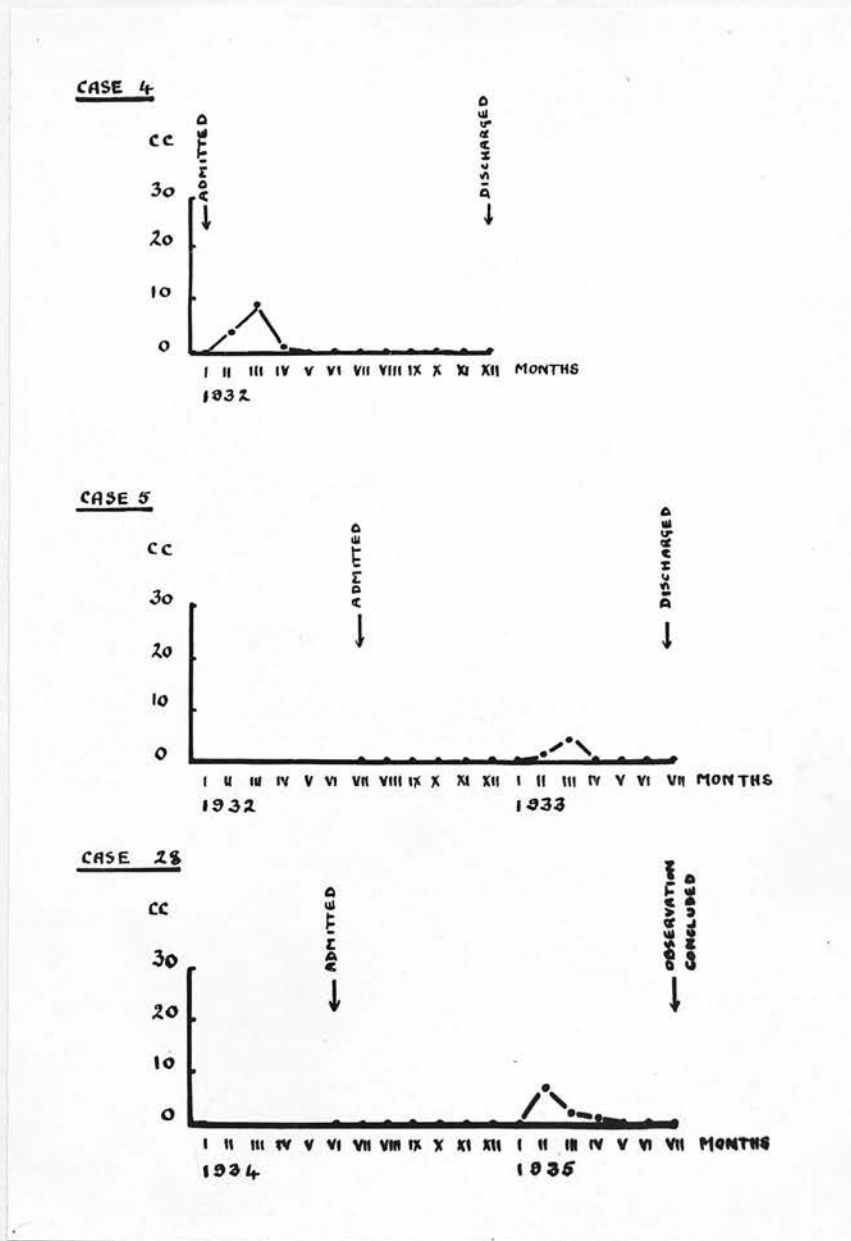


Figure 6.- The average daily volume of expectoration for each month of a complete year in three illustrative cases. (Details in Appendix I.)

Figure 6 depicts the results of the investigation in three patients who, except for a brief period/

period, expectorated no sputum whatever. It is worthy of note, however, that the short periods during which some expectoration was present embraced the months of February, March and April only. In all cases *B. tuberculosis* was successfully demonstrated in the sputum.

It is not claimed that all cases exhibited seasonal variation comparable to the six examples illustrated above. In a proportion of cases (5 out of 31) the maximum expectoration was autumnal whilst a still larger number were the subjects of a minor rise in the amount of sputum about that time. It was necessary therefore, to construct a curve based on the mean for the entire number of cases. In order to do this the amount of sputum expectorated for each month was recorded as a percentage of the total amount for the year. The necessary calculations were made for each of the 31 cases, and the mean of all cases for each month of the year was computed. In those patients who formed the subject of this observation for more than one year, two recordings were available for each month in excess of the year. In such a case the mean of these two readings was taken as the starting point for the above calculations. An example will make this clear. Case 6 (vide Appendix I, Table 1, page 231) was in residence for thirteen months, from May 1932 to May 1933. Two readings therefore existed for the month of May. The average daily output of/

of expectoration was 14 cc. in May 1932, and 5 cc. in May 1933. In order to make the calculation on an annual basis, the daily volume of sputum for the month of May was taken to be 10 cc. which is (to the nearest whole number) the arithmetic mean of the available data for the month of May. Admittedly this method would not be acceptable to the biometrician who would consider it necessary to estimate the amount of variation from day to day and to compare it with the variation from month to month before drawing any conclusions. The labour involved in 31 cases is however enormous, and probably does not justify the exclusion of the relatively slight margin or error which exists in the present method. The results are to be found in Appendix I, Table 2, page 233.

The average degree of seasonal variation in the abundance of expectoration in the above 31 cases of pulmonary tuberculosis is recorded in Table 3, and also in Figure 7 (page 32).

Table 3.- The percentage amount of expectoration for each month of the year in 31 cases of pulmonary tuberculosis.

Month	Sputum: percentage amount	Month	Sputum: percentage amount
I	8.1	VII	5.8
II	12.6	VIII	7.5
III	14.6	IX	7.9
IV	10.8	X	7.0
V	6.7	XI	6.8
VI	5.7	XII	6.5

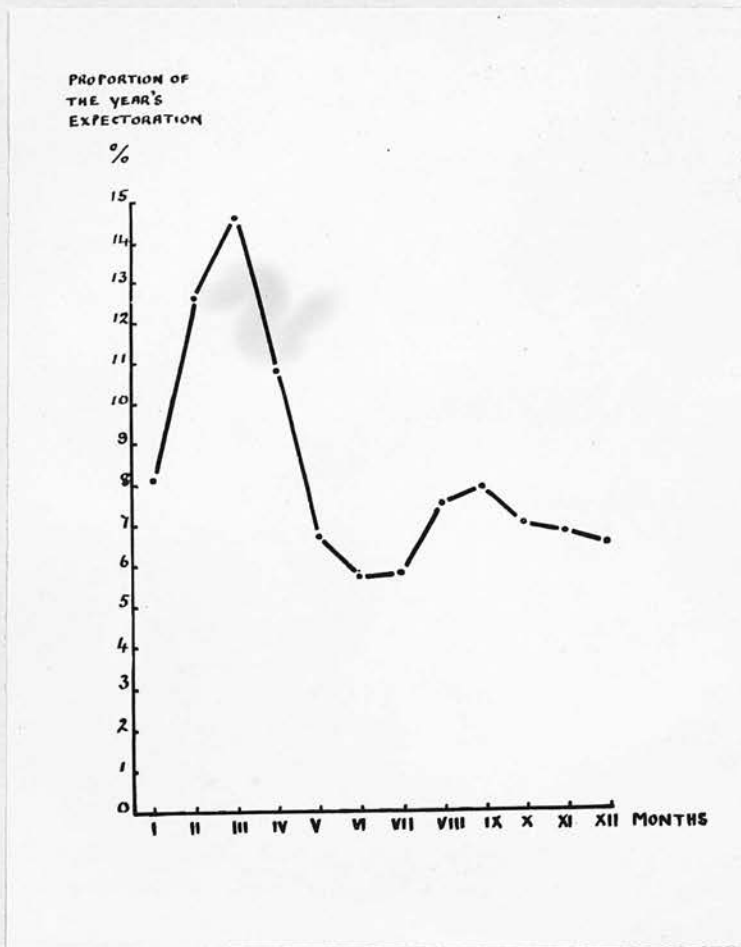


Figure 7.- Seasonal variation in the amount of expectoration in pulmonary tuberculosis. The data represented in the above Figure are based on daily measurements in 31 cases for at least 12 consecutive months.

From the data expressed in Table 3 and Figure 7 it will be seen that a marked seasonal fluctuation in the amount of sputum occurred in these cases. The maximum output was noted in February, March and April, and the minimum in June and July. The most notable point, however, is the remarkable discrepancy between the highest and lowest recordings. Most clinical/

clinical observers would question the accuracy of the statement that owing to seasonal variation the amount of sputum which cases of pulmonary tuberculosis expectorate in the month of March is almost two and a half times as great as that expectorated in June and July. A scrutiny of the results in individual cases, however, (Appendix I, Table 2, page 233) reveals the fact that three particular patients were largely responsible for this surprisingly pronounced degree of seasonal change. These cases have already been illustrated in Figure 6 (page 29), and constitute a group in which all the sputum for the year of observation was expectorated during the months of February and March, or February, March and April. In case 5, for instance, 80 per cent. of the sputum for the year was expectorated during March, whilst in case 28, 70 per cent. was produced in February, but in neither of these cases was the sputum at any time abundant. In order to eliminate the enormous relative importance of a small absolute increase in sputum in a case previously without expectoration, the three patients referred to above were removed from the series, and the average seasonal variation recalculated for the remaining 28 patients. The results are presented in Table 4 and in Figure 8 (page 34).

From the recorded results a less pronounced but still marked seasonal trend can be observed in the volume of sputum expectorated by these patients.

Table 4.- The percentage amount of expectoration for each month of the year in 28 cases of pulmonary tuberculosis.

Month	Sputum: percentage amount	Month	Sputum: percentage amount
I	9.0	VII	6.4
II	9.8	VIII	8.3
III	10.3	IX	8.7
IV	11.3	X	7.8
V	7.4	XI	7.5
VI	6.3	XII	7.2

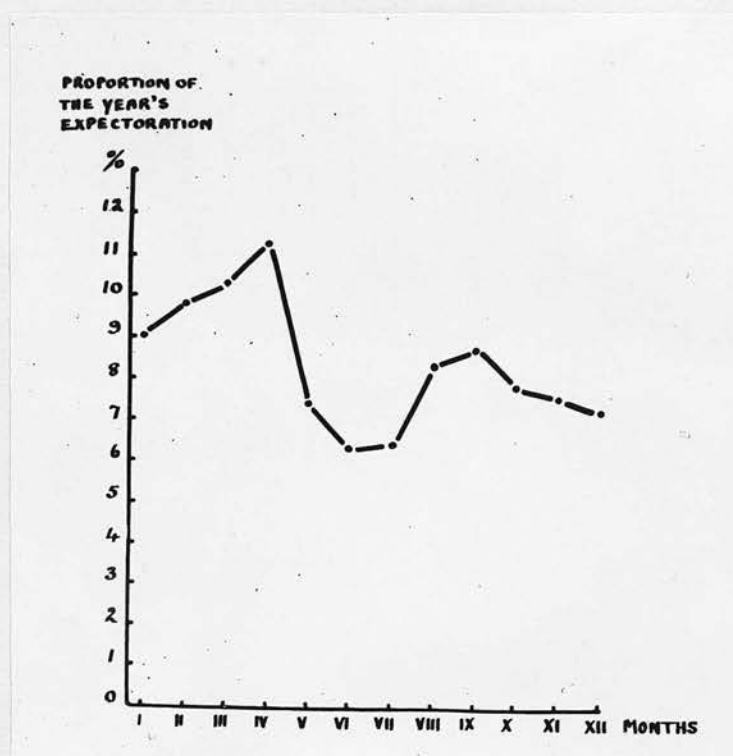


Figure 8.- Seasonal variation in the amount of expectoration in pulmonary tuberculosis. The data represented in the above Figure are based on daily measurements in 28 cases for at least 12 consecutive months.

Table 4 and Figure 8 indicate that a steady/

steady increase occurred in the amount of sputum expectorated during the spring reaching a maximum in April. During the summer a rapid diminution ensued and a comparatively small proportion was expectorated during June and July. An increase occurred in August, but the remaining monthly values were in close approximation to the proportions which might be expected in the absence of any seasonal change. The increase in the expectoration in March and April remained the most pronounced feature of the curve.

Conclusion.- In pulmonary tuberculosis, as in glandular tuberculosis, the softening of lesions is more in evidence during March and April than at other times of year.

THE SEASONAL INCIDENCE OF HAEMOPTYSES
IN PULMONARY TUBERCULOSIS

Introduction.- Some evidence already exists which would seem to show that haemoptyses in pulmonary tuberculosis are more likely to occur at certain times of year than at others. A short note by Brinkmann (1928), which has been referred to elsewhere (page 8), mentions a spring-time incidence. Burns (1922) found that in Boston haemoptyses were more likely to occur in hot weather notably in June. Anders of Philadelphia has studied the possibility extensively. In his first communication (1907) he analysed 157 personal cases and stated that the incidence of haemoptyses was most marked during the late spring and summer. In a wider investigation however (1909), he found that December, January and February formed the period during which haemoptyses occurred most frequently.

An opportunity to test these observations was afforded by the examination of the case histories of a large number of patients suffering from pulmonary tuberculosis who were resident in Southfield Sanatorium Colony or attending the Tuberculosis Clinic of the Royal Infirmary, Edinburgh.

Selection of Cases.- For the purposes of the present investigation haemoptysis was taken to mean the expectoration of fluid blood by a patient/

patient suffering from pulmonary tuberculosis in whom there was no cardiac lesion which might of itself be the cause of blood spitting. No consideration was devoted to blood streaked sputum. The origin of such staining is too doubtful to allow it to be classed as pulmonary haemorrhage.

In glandular tuberculosis mention was made that there was occasionally some difficulty in establishing the exact date when the disease first attracted attention. But in patients suffering from pulmonary tuberculosis there was little difficulty in determining the precise date of an haemoptysis. Bleeding of this kind is not readily forgotten, and in the majority of instances occurred whilst the patient was actually under observation.

In four cases a second haemorrhage occurred exactly a year after the first. Five patients experienced repeated haemorrhages in rapid succession, but the date of onset only was taken into account, and the bleeding was judged to be a single haemorrhage. Manifestly if, in patients who were the subjects of many haemorrhages throughout several months, each recurrence were included in this inquiry, a preponderance of haemoptyses would be falsely attributed to a certain time of year. This would be a serious inaccuracy. On the other hand, in patients in whom a second haemopytsis occurred after a year's apparent quiescence, a seasonal incidence is definitely/

definitely suggested.

Classification and Results.- In this investigation 216 haemorrhages were recorded in 212 patients. These haemorrhages were divided into twelve groups according to the month of the year during which each occurred. The monthly incidence is illustrated in Figure 9. There is apparently a slight increase in

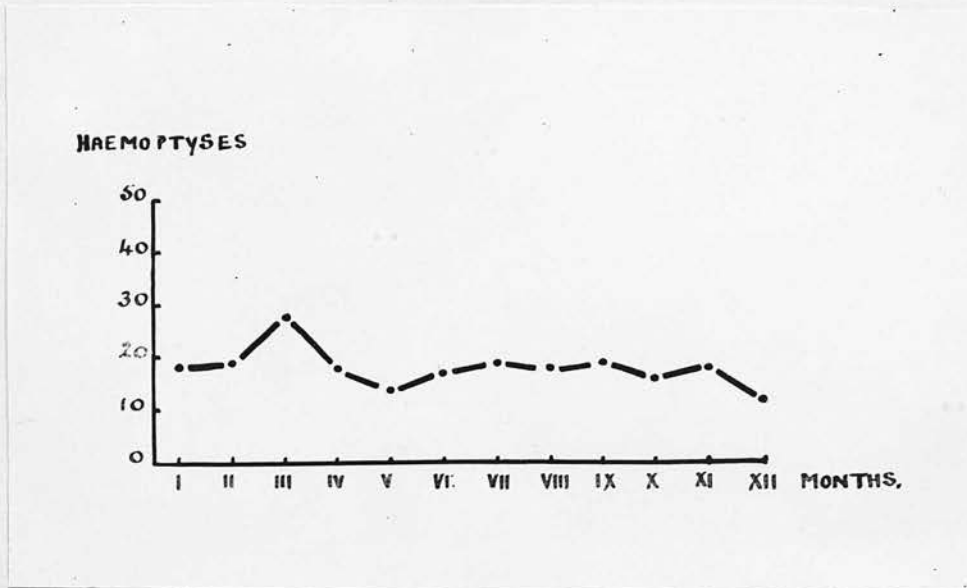


Figure 9.- The monthly distribution of 216 haemoptyses observed in 212 cases of pulmonary tuberculosis.

the frequency of haemoptyses in the month of March, but for the most part, the distribution throughout the year is remarkably uniform. From the facts as presented in Figure 9 no deduction can be made as to whether there is a seasonal trend in the occurrence of haemoptyses.

Conclusion.- From the available material it/

it is not possible to state if there is any seasonal variation in the incidence of haemoptysis in pulmonary tuberculosis.

SEASONAL VARIATION IN TUBERCULOUS LESIONS

Conclusions.-

1. The appearance of glandular enlargement in tuberculosis of the lymphatic system occurs most commonly during the months of January and February, and least commonly in August and September.

2. Pus formation in tuberculous glands is particularly frequent in March and April, but relatively uncommon during August, September and October.

3. In pulmonary tuberculosis expectoration is more copious in March and April, and more scanty in June and July than at other times of year.

4. A seasonal tendency in the incidence of haemoptyses has not been apparent.

PART IISEASONAL VARIATION IN THE SYSTEMIC FACTOR
IN TUBERCULOSIS

It would be surprising if the seasonal tendency to the ripening of lesions which has been described in glandular and pulmonary tuberculosis, did not have its repercussions in corresponding fluctuations in various systemic manifestations of the disease. Part Two of this work was therefore undertaken to discover to what extent tuberculous intoxication did, in fact, vary at different times of year.

Only certain indications of toxaemia can be recorded with sufficient accuracy to permit of continuity of comparison throughout a period of time. Broadly speaking, only those manifestations of intoxication which were capable of being expressed by means of figures were of service in this inquiry. Thus, the body temperature, the state of the circulation as shown in the pulse rate, the body weight, and finally the reaction to tuberculin were considered to be promising subjects of investigation. The data were collected from patients suffering from all forms of tuberculosis, who were undergoing treatment at Southfield Sanatorium Colony, Edinburgh.

SEASONAL VARIATION IN THE BODY TEMPERATURE
OF TUBERCULOUS SUBJECTS

Introduction.- Fever is not an essential feature of tuberculosis. Many patients may go through the whole course of the disease without experiencing any disturbance of body temperature. Frequently, however, the instability of the heat regulating mechanism permits slight rises of temperature to occur from relatively trivial causes. Only exceptionally among sanatorium patients is the temperature curve distorted by high fever.

But even including these febrile cases, it may be stated that for the most part the body temperature in tuberculosis lies between 96° and 103°F., the usual range, however, being from 96° to 98°F. In the following investigation it is proposed to ascertain in what proportion the temperature varies between these limits at different times of year.

Method of Investigation: Selection of Cases.-

The temperature record was analysed of every patient who was in residence at Southfield Sanatorium Colony for one or more years. The number of these patients was 186, and the total number of completed years represented by their combined period of treatment was 255.

In all patients the temperature was taken twice a day, namely at seven o'clock in the morning and/

and five o'clock in the evening. The axillary method was employed, and the thermometer was left in position for at least five minutes before the temperature was recorded. No additional two-hourly or four-hourly readings were included in this series of observations since such a procedure would have incorporated an undue proportion of febrile readings from an intoxicated group of patients. Two-hourly and four-hourly charts are only used in Southfield Sanatorium Colony if a patient's temperature is over 100°F. or if there is some other special reason. In the series of patients who formed the material for this study the temperature was recorded on 184,424 occasions.

Details of the Method of Analysis.- These individual recordings were classified according to the time of year and the degree of pyrexia. The customary divisions of the Fahrenheit temperature scale were adopted, and the temperature readings for each month were classified in the following seven divisions.- 96° to 96.8°; 97° to 97.8°; 98° to 98.8°; and so on up to 102° to 102.8°F. Any temperature registered below 96°F. was allotted to the first of the above groups, and any records of 103°F. or more were included in the highest group.

Presentation of Results.- The seasonal variation in the temperature of tuberculous patients as revealed by the above method of analysis will be considered under the following headings- (1)/

- (1) Seasonal Variation in Body Temperature as noted in All Cases.
- (2) Seasonal Variation in the Body Temperature of Adult Patients.
- (3) Comparison of the Seasonal Variation in Body Temperature Occurring in Male and Female Adult Cases.
- (4) Seasonal Variation in the Body Temperature of Children.

(1) Seasonal Variation in the Body Temperature of Tuberculous Subjects Based on a Study of All Available Cases, Adults and Children of Both Sexes.- The analysis of 184,424 temperature recordings demonstrated in yet another way the great importance of the spring months to the tuberculous patient. The result of the analysis is shown in Table 5, and also in Figure 10.

Table 5.-/

Table 5.- The analysis of 184,424 temperature recordings according to the degree of pyrexia and the time of year.

Month	96°-	97°-	98°-	99°-	100°-	101°-	102°-	Total
I	5630	7268	2229	380	78	20	10	15615
II	5052	6188	2386	435	135	45	30	14271
III	4886	6277	3412	689	253	107	34	15658
IV	5003	6707	2672	587	147	60	32	15208
V	5582	7339	2143	367	127	55	23	15636
VI	5188	7439	2058	335	77	31	7	15135
VII	5717	7588	2066	228	59	22	11	15691
VIII	5358	7722	2259	228	43	19	5	15634
IX	5674	7257	1893	251	41	14	2	15132
X	6173	7205	2022	231	29	15	6	15681
XI	5791	6974	2055	294	42	11	0	15167
XII	5997	7229	2003	284	61	21	1	15596
Total	66051	86193	27198	4309	1092	420	161	184424

It will be seen from Table 5 that the number of occasions on which temperatures of 98°F. and upwards/

upwards were recorded was greater during the spring months than at other times of year, and greatest of all in the month of March; whilst at the same time the same time the number of readings from 96° to 97.8°F . diminished correspondingly. There occurred, in other words, a "shift to the right" during the spring of the year.

The graphic representation of all the data contained in the above table would have resulted in so complicated a figure that accurate interpretation would have been difficult. Therefore only the more important features in Table 5 have been depicted graphically (vide Figure 10, page 46). The proportion of temperature readings above 100°F . was very small and was neglected. But the average number of temperatures recorded throughout the year between 98° and 99.8°F . which included the uppermost limits of normality and the region of mild fever, amounted to 17 per cent. of the total, and this number received special attention.

In Figure 10 the abscissa represents the time of year, and the ordinate the number of temperature recordings. The upper curve denotes the number of occasions on which temperature readings between 98° and 98.8°F . were recorded, and corresponds to column 4 in Table 5. The lower curve represents the number of occasions on which temperature readings were registered between 99° and 99.8°F . and corresponds to/

to column 5 in Table 5.

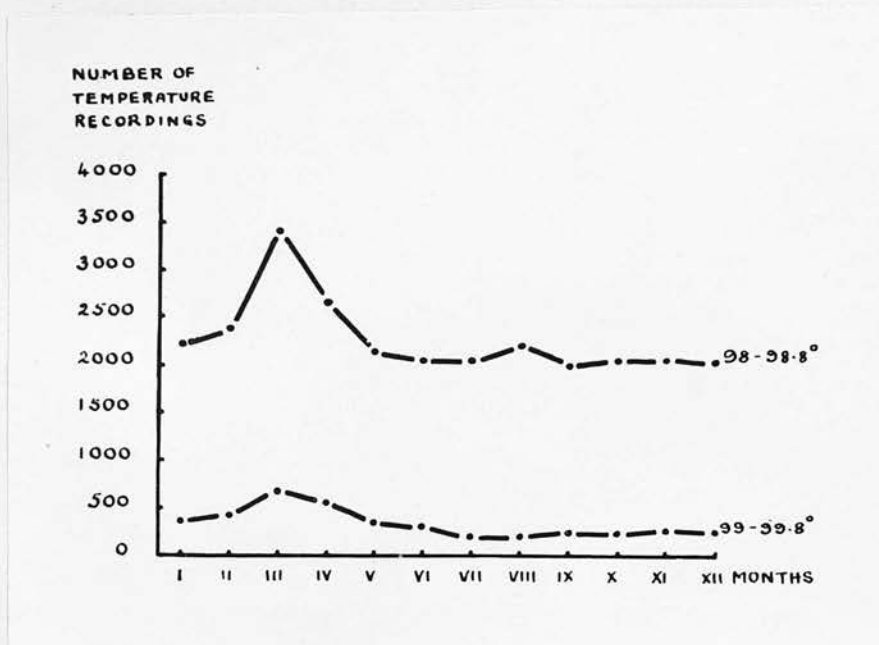


Figure 10.- The number of occasions per month on which temperatures of 98° to 98.8°F. and 99° to 99.8°F. were recorded in 186 tuberculous subjects. The data represented in this graph were derived from an analysis of 184,424 temperature recordings.

It will be seen that, during the greater part of the year, from 2,000 to 2,400 temperature recordings per month were noted between 98° and 98.8°F. and about 250 to 350 between 99° and 99.8°F. During the months of March and April, however, these numbers were greatly increased, indicating a more frequent disturbance of the body temperature at this time.

The method of representation of the same findings adopted in the construction of Figure 11 (page 48) probably gives a more accurate picture of the above noted variation, since due allowance is made for the fact that the calendar months are not all of equal/

equal length. It should be particularly noted that the total number of temperature readings for the month of February which has only 28 days, was 10 per cent. less than the number of readings taken during months of 31 days. It will be seen from Figure 10, however, that despite this very considerable reduction in the total readings for February, the number of occasions on which the temperature was recorded between 98° and 98.8°F. and also between 99° and 99.8°F. was slightly in excess of the number for January. It follows therefore that the actual proportion of temperature readings occurring within these limits during the month of February must have been decidedly greater than is apparent from a study of Figure 10.

The simplest way to adjust the data for each month in order to render them comparable with one another, was to estimate the proportion of the total readings for each month which was registered between 98° and 98.8°F. and between 99° and 99.8°F. This was calculated on a percentage basis. The results are presented in Figure 11 and also recorded in Appendix II, Table 2, (page 236). The ordinate in Figure 11, and in subsequent Figures records the percentage number of the temperature readings for the month noted between the stated limits.

Reference to Figure 11 now reveals a seasonal variation in the body temperature very similar to/

to that previously noted, but it will be observed that the relative increase in the frequency of febrile disturbances during the month of February was considerably greater than might be supposed from the curves in Figure 10. It may be stated that the body temperature

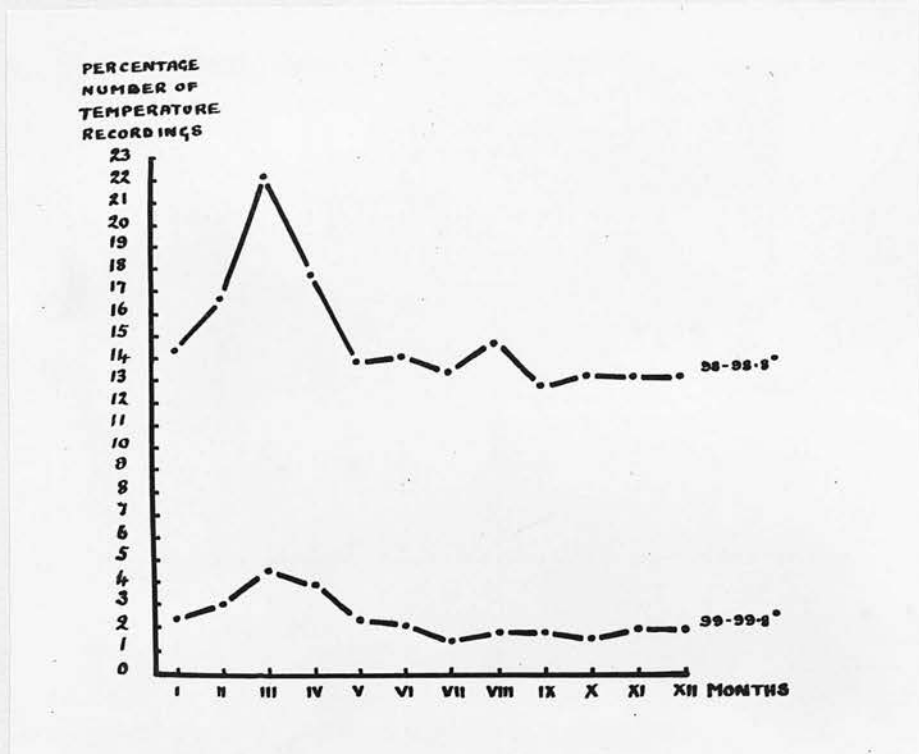


Figure 11.- The percentage number of temperature recordings for each month of the year observed between 98° and 98.8°F. and between 99° and 99.8°F. The data represented in this graph were derived from an analysis of 184,424 temperature recordings.

exhibited the first signs of unusual instability in the month of February. During March this tendency was at its height, whilst in April the disturbances of temperature were again less pronounced. The number of supra-normal recordings for the month of May was/

was approximately equal to the average for the rest of the year.

(2) Seasonal Variation in the Body Temperature of Adult Tuberculous Patients.- Before proceeding further with the analysis of the data obtained from the case histories as outlined above, it became necessary to withdraw from the main series of cases a small group of highly intoxicated adult patients who were the subjects of excessive fever for long periods. This procedure eliminated eight male patients and three female patients in all of whom the clinical classification was L₃S throughout the whole period of observation. The remaining cases could now be divided into sexes giving subgroups comparable with one another.

It is possibly worthy of mention, however, that these very toxic patients exhibited much the same seasonal variation in body temperature as was observed in the main group of cases, but of a more pronounced degree. The "shift to the right" in these more advanced cases was especially noticeable from 100°F. upwards, and indeed there were numerically a greater number of readings above 100°F. in these 11 patients than in the entire main group of 175 cases. The analysis of the figures for this small group of patients is to be found in Appendix II, Table 3, (page 236).

Eleven cases is not a large number, and it might at first sight be thought that their removal was an unnecessary refinement. But since the eight thousand temperature readings in these cases were almost all elevated, and distributed between male and female patients in the proportion of eight to three, it was essential to discount this source of inaccuracy before comparing the sexes in a subsequent section.

The adult group of cases now numbered 99, and represented a total period of treatment of 132 years, during which time the temperature was recorded on 97,915 occasions. The complete analysis of the temperature records is to be found in Appendix II, Tables 4 and 5, (page 237).

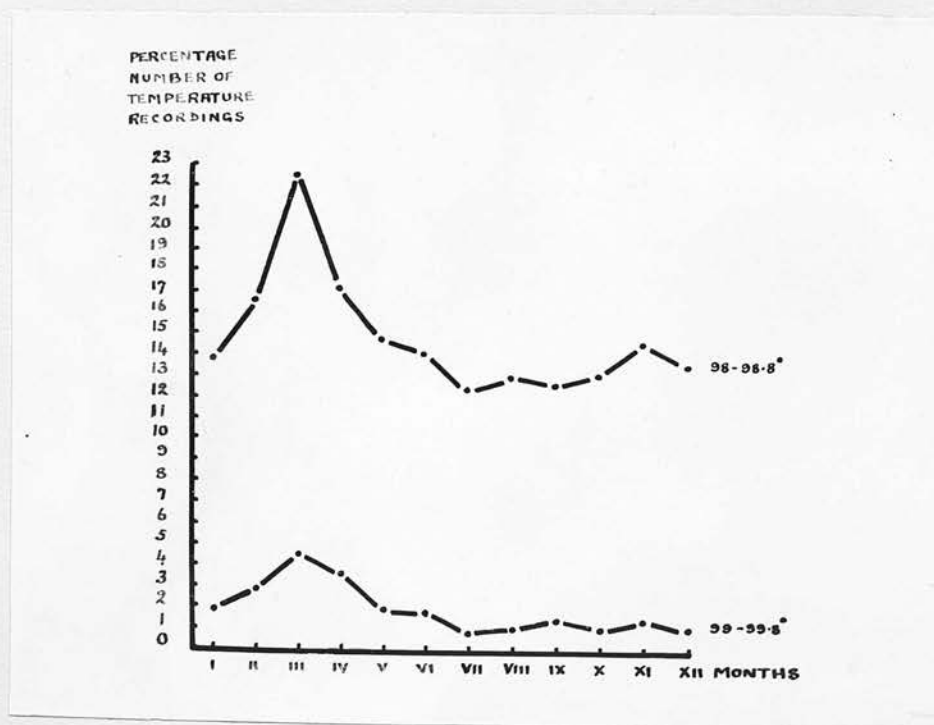


Figure 12.- Seasonal Variation in the body temperature of adult tuberculous patients. The data are based on 97,915 temperature readings.

The results have also been recorded graphically in Figure 12 (page 50). It will be seen that in the adult group of cases the instability of the body temperature during the months of February, March and April was again encountered. The results were closely similar to those exhibited by the entire group of cases.

(3) Comparison of the Seasonal Variation Occurring in Adult Male and Female Tuberculous Patients.- The analysis of the available data was taken a stage further in order to compare the seasonal variation in body temperature in the two sexes. There were found to be 51 male patients giving a total period of treatment of 70 years, and 50,313 temperature recordings. There were 48 female patients in whom the duration of residence amounted to 66 years during which time the temperature was taken on 47,602 occasions.

The complete details of the monthly variation from 96°F. upwards may be consulted in Appendix II, Tables 6 to 9, (page 238). But the most important points are depicted graphically in Figure 13, (page 52). It will be noted that whilst the essential features of the seasonal change were present in both sexes, certain important differences must be described.

The most striking difference was the extent to which febrile disturbances occurred during the spring/



spring months in female as compared with male patients.

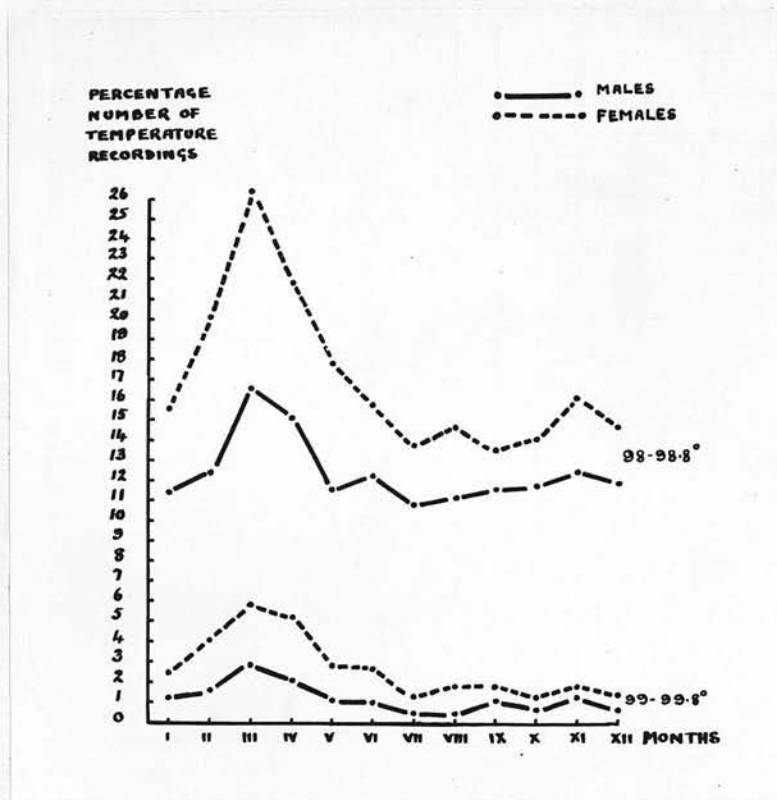


Figure 13.- Seasonal variation in the body temperature of male and female tuberculous patients. The curves in this graph are based on 50,313 temperature recordings in male cases and on 47,602 recordings in female cases.

In the first place, however, attention should be drawn to the fact that throughout the whole year more temperatures were recorded between 98° and 99.8°F. (and, as will be seen from the Tables referred to in Appendix II, correspondingly fewer between 96° and 97.8°F.) among the females than among the males. Thus if the months of February, March and April be excepted, Figure 13 shows that among the male sex approximately 11 to 12 per cent. of the temperature/

temperature readings for each remaining month were recorded between 98° and 98.8°F . whilst the corresponding figure for the females was 13 to 17 per cent. Similarly, temperatures between 99° and 99.8°F . were always found more frequently in the female sex than in the male. Apparently therefore, slight disturbances of temperature were more common in female cases than in male cases.

The reasons for this difference are probably closely related to the peculiarities of the female physiology. Thus, before and possible during menstruation the temperature of the normal woman is said to rise 1° or even 2°F . Likewise, in the majority of human beings emotional causes are apt to raise the temperature to a similar extent, though this is more commonly observed in women than in men. Anyone who is associated with anti-tuberculosis work appreciates the frequency with which the temperature of women patients may be upset by these two factors. Herein lies, in all probability, the explanation of the frequency with which the temperature in female cases was found to be higher than that of a similar group of male patients.

But during the spring this difference between the sexes increased quite disproportionately. Figure 13 shows that in the month of March the number of temperature readings between 98° and 98.8°F . was 16.6 per cent. in the male cases and 26.4 per cent in the/

the female cases. Similarly also, a much larger proportion of readings between 99° and 99.8°F. was registered among the female cases than among the male.

The relative difference between the sexes in this respect is summarised in Table 6 . In this Table the range of temperature from 98° to 99.8°F. is considered, without reference to two smaller divisions, in order to simplify the construction of the table.

Table 6.- Comparison of seasonal variation in body temperature in male and female patients.

Percentage number of temperature readings observed from 98° to 99.8°F. during the spring (a), and during the rest of the year (b).		Males	Females
(a)	16.92	28.08	
(b)	12.52	17.00	
Calculated percentage of readings in the female cases which would have been noted in the spring if the seasonal increase had been the same as that of the male cases.			22.97

The extent to which the sexes differed is indicated in the lowest line of the table, which shows the calculated proportion of temperature readings which was to be expected in the female sex if the seasonal change had been the same as in the male sex. The expected figure was 22.97 per cent. The actual/

actual figure was 28.08 per cent. It would appear therefore, that the seasonal variation in the body temperature of female tuberculous subjects was greater than that observed in male cases.

This deduction, however, cannot be accepted without further investigation. Despite the fact that the male and female groups of cases were rendered comparable as far as possible by the exclusion of an unequal number of highly intoxicated cases in each sex, the possible explanation of the results in Figure 13 and in Table 6 remains two-fold. Either the seasonal reaction in body temperature was more frequently encountered in the female sex, or else the apparent difference between the sexes was due to an unusually marked response to the spring of the year on the part of a relatively small number of female cases.

If subsequent investigation confirms the former hypothesis it may be concluded that the female sex is more susceptible to seasonal variation in the body temperature in tuberculosis than the male. On the other hand, if the latter alternative is found to hold good no such inference might be drawn. It was necessary therefore to ascertain the degree of seasonal response in each patient, and to compare the sexes in respect of the number of cases in which the seasonal variation in the temperature was absent, slight, moderate or marked.

In compiling the data which were recorded/

recorded collectively in Table 5 (page 44), similar tables had been prepared for each individual patient. These tables were now all re-examined and classified according to the intensity of the seasonal change observed in each.

To describe completely the methods by which the standards of variation were determined would necessitate a very lengthy digression. The data for ten illustrative cases however, are presented in Table 7 which will furnish an indication of the standards ultimately adopted (page 57).

In the first three cases represented in Table 7, no seasonal variation was apparent either on account of the small number of readings above 98°F. or the negligible differences between the spring and the rest of the year. In cases 4, 5 and 6 seasonal variation in the temperature was considered to be present since the difference between the spring and the rest of the year was quite definite. Cases 7 and 8 are examples of a more pronounced seasonal change, whilst cases 9 and 10 illustrate the extreme type of reaction which was occasionally encountered.

When all the available records were thus examined, which, it will be recalled, amounted to 70 in male cases and 66 in female cases, the numbers exhibiting seasonal variation in temperature or alternatively exhibiting no such variation at all, were recorded in Table 8, (page 58).

Table 7.- Cases illustrating the varying degrees of seasonal variation of the body temperature of tuberculous subjects. The number of temperature recordings in different degrees are compared during the spring and the rest of the year. The seasonal variation is described as negative (-) or positive (+, ++, +++).

(a) = spring

(b) = rest of year

Case Number and Name	Average monthly number of temperature recordings during (a), (b)	98°	99°	100°	101°	Observed seasonal variation
1 A.A.	(a)	4	0	0	0	negative
	(b)	1	0	0	0	
2 D.J.M.	(a)	12	0	0	0	negative
	(b)	8	0	0	0	
3 D.McD.	(a)	27	3	0	0	negative
	(b)	19	2	0	0	
4 C.C.	(a)	8	0	0	0	positive +
	(b)	0	0	0	0	
5 M.K.	(a)	17	2	0	0	positive +
	(b)	7	1	0	0	
6 M.D.	(a)	33	20	0	0	positive +
	(b)	29	3	0	0	
7 R.M.	(a)	20	6	0	0	positive ++
	(b)	10	1	0	0	
8 N.R.	(a)	30	10	0	0	positive ++
	(b)	20	2	0	0	
9 T.B.	(a)	16	13	6	2	positive +++
	(b)	9	2	0	0	
10 A.S.	(a)	14	19	10	6	positive +++
	(b)	8	12	2	0	

Table 8.- The number of yearly records in which adult cases of both sexes exhibited or failed to exhibit seasonal variation in temperature.

Sex		Male	Female
Number of cases		51	48
Total number of years of records		70	66
Yearly records exhibiting no seasonal variation		44	30
Yearly records exhibiting seasonal variation.-	+	15	19
	++	6	12
	+++	5	5
	Total	26	36

It will be seen, on reference to the above table, that a greater number of female cases were the subjects of seasonal variation in temperature than male cases. But since the number of years of records during which patients of the two sexes were observed were not equal, it was necessary to express the data in Table 8 on a percentage basis in order to allow of accurate comparison between male and female cases. The results of this procedure are presented in Table 9 (page 59).

Table 9/

Table 9.- The number of yearly records, tabulated on a percentage basis, during which adult cases of both sexes exhibited or failed to exhibit seasonal variation in temperature.

Sex		Male	Female
Percentage of yearly records exhibiting no seasonal variation.		62.9	45.5
Percentage of yearly records exhibiting seasonal variation.-	+	21.4	28.8
	++	8.6	18.2
	+++	7.1	7.5
	Total	37.1	54.5

From Table 9 it may be seen that a greater proportion of female cases were the subjects of seasonal variation in temperature than male cases. It was found that whilst this variation was only observed in 37.1 per cent. of the male cases, it was present in 54.5 per cent. of the female cases. This difference between the sexes was chiefly noted in the moderate degrees of seasonal change (designated +, and ++ in Table 9), whilst cases demonstrating excessive fluctuations (designated +++ in the table) occurred almost equally in the two sexes.

The probability is, therefore, that in adult patients suffering from tuberculosis, the seasonal change in the body temperature is observed more frequently in the female sex than in the male.

(4) Seasonal Variation in the Body Temperature of Tuberculous Children.- The following investigation was based on the analysis of the records of 76 children in whom the total duration of residence amounted to 108 completed years. The average age of the patients was $6\frac{1}{2}$ years. In this group of cases the temperature was recorded on 78,496 occasions.

The tabular representation is to be found in Appendix II, Tables 10 and 11, (page 240). The proportion of temperature readings noted between 98° and 99.8°F. at different times of year is shown graphically in Figure 14.

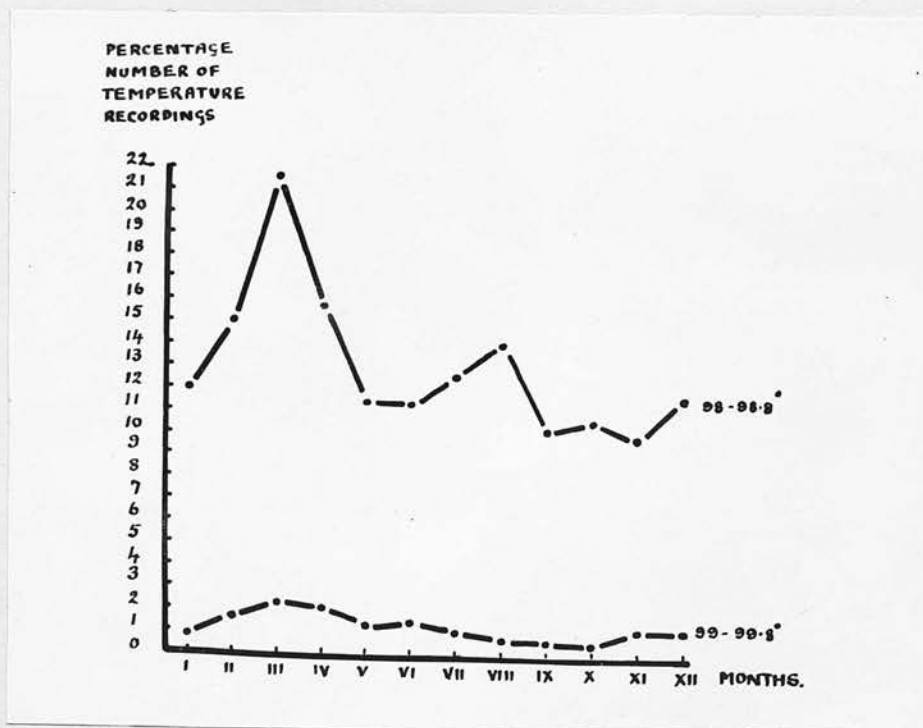


Figure 14.- Seasonal variation in the temperature of tuberculous children. The curves in this graph are based on the analysis of 78,496 temperature recordings.

In Figure 14 the upper curve, denoting the proportion of temperatures between 98° and 98.8°F. shows the typical spring-time reaction, similar to but slightly more pronounced than that noted in adult patients. A slight secondary rise in July and August demonstrated the effects of the two warmest months of the year in causing slight temperature reactions.

The lower curve in this figure showed that temperature readings between 99° and 99.8°F. were registered much less frequently at all times of year than in adult cases. Lest this result seem surprising in view of the rather unstable nature of the child's temperature, it should be pointed out that taking the cases as a whole, the children constituted a group of patients in whom the prognosis was more generally favourable than in the adult group. There were, for example, a large proportion of cases of early glandular tuberculosis in whom little or no systemic upset was noted, and also a number of cases with no active lesion, which were admitted for anticipatory detuberculation. It was not, therefore, surprising that mild fever occurred less frequently throughout the year in these children, than in a group of adult patients in whom more gross lesions were the rule.

But the actual seasonal fluctuation observed in the incidence of temperature readings between 99° and 99.8°F. was no less marked in the children than in the adults, and such readings were noted more than/

than twice as frequently during the spring months as during the rest of the year.

It is clear, therefore, that in children as in adult patients, the temperature is more unstable during the spring than at other times of year.

Conclusions.-

(1) A seasonal variation occurs in the body temperature of patients suffering from all forms of tuberculosis. During the months of February, March and April febrile disturbances of varying degrees are more frequently recorded than at other times of year, but the tendency is most marked in the range of temperatures from 98° to 99.8°F.

(2) The above noted variation is present in both adult patients and in children.

(3) In adult cases the female sex is more susceptible to the variation in body temperature than the male sex.

SEASONAL VARIATION IN THE PULSE RATE OF THE
TUBERCULOUS SUBJECT

Whilst the data concerning the seasonal variation in the temperature of tuberculous subjects were being collected, similar information regarding the pulse rate was also obtained in an endeavour to ascertain what change, if any, was observable in the circulation of these patients at different times of year.

It soon became apparent, however, that the day to day variation in most patients was so pronounced, that no periodicity of the type noted in the body temperature was detectable. This was not surprising for the volatility of the pulse rate in tuberculosis is well known, and many minor factors which were incapable of affecting the temperature, had nevertheless a disturbing effect on the circulation.

After the analysis of 86,225 pulse rate recordings with negative results it was decided not to proceed any further with the time consuming task. The results obtained were representative of 33 men, 33 women and 26 children. For this group of patients the total period of treatment amounted to 120 completed years. The analysis of the results is shown in Table 10.

Table 10/

Table 10.- The analysis of 86,225 pulse recordings according to time of year and pulse rate.

Month	Pulse rate per minute							Total
	60-	70-	80-	90-	100-	110-	120-	
I	294	859	2459	2823	878	136	23	7472
II	242	862	2424	2456	675	40	17	6716
III	322	903	2261	2657	925	124	51	7243
IV	283	1142	2274	2352	850	169	44	7114
V	395	1085	2214	2509	908	177	20	7308
VI	398	1153	2108	2508	818	92	18	7095
VII	372	1290	2257	2308	981	93	12	7313
VIII	457	1377	2125	2302	960	142	18	7381
IX	370	1269	2231	1966	974	194	21	7025
X	412	999	2490	2295	893	150	23	7262
XI	279	891	2519	2414	717	221	22	7063
XII	303	1008	2694	2371	712	128	17	7233
Total	4127	12838	28056	28961	11291	1666	286	86225

In the above table columns 2 to 8 indicate the number of pulse rate recordings between 60 and 120 beats per minute. Any recordings below 60 per/

per minute were included in column 2, whilst those above 120 per minute were included in column 8. It will be seen from the table that no seasonal variation in the pulse rate corresponding to the change previously noticed in the temperature was present, unless in the incidence of readings of 120 or more per minute which closely followed the seasonal fluctuation noted in the higher degrees of fever. In this category, however, numbers were so small as to make any inferences unreliable.

As stated above, this finding was probably due to the fact that the pulse rate in tuberculous patients was influenced by so many factors that any tendency to seasonal change was completely masked by minor occurrences which caused great variation from day to day.

Conclusion.- The evidence available does not indicate that there is a seasonal variation in the circulation of tuberculous patients as observed in a study of the pulse rate.

SEASONAL CHANGE IN THE WEIGHT OF
TUBERCULOUS SUBJECTS

Introduction.- The writer makes no apology for re-introducing a theme which has formed the subject of many a previous study. Not only is the body weight of cardinal importance in any consideration of the systemic factor in tuberculosis, but the present method of investigating seasonal variation in weight is new, and affords results somewhat different from those which have already been recorded.

Various observers have advanced evidence which would seem to indicate that tuberculous patients, undergoing suitable treatment, gain weight at all times of year, but not so rapidly in the spring as in the autumn. The majority of investigators based their conclusions on calculations of the average weekly or monthly gain in weight in the various institutions under their control. (Strandgaard, 1922, 1932; Fridmodt-Muller, 1932; Pai, 1929; Philips, 1933; Stallybrass, 1928; Stub-Christisen, 1931.) Similar results in tuberculous children have also been noted (Orel, 1926).

Minor differences appeared in the results of the various authors, but were for the most part, due to the different latitudes in which the several investigations were conducted. Thus, in Norway the maximum body weight is said to occur in August or September/

September (Lunde, 1925). In Denmark similar observations were made by Strandgaard in both his publications. In Madras, on the other hand, the weight of tuberculous subjects is greatest in November; (Fridmodt-Müller, 1923, and Pai, 1929). Strandgaard (1932) in his most recent paper on the subject, elaborated this relationship of seasonal change in body weight to latitude, and summarised his findings by stating that the maximum body weight in northern countries occurred in August, and that in progressively lower latitudes it was noted in September, October and even in November. In the southern hemisphere the process was reversed. In the Argentine, in fact, the body weight of tuberculous subjects was greatest during the period from March to May.

It is not intended to anticipate more formal discussion (page 172) by inquiring, at the present moment, into the cause of seasonal variation in weight, but in order to complete this short review, the current views may be briefly stated.

Strandgaard, whose observations incorporate the collected data from eight sanatoria, formed the opinion that the factors of greatest consequence were meteorological, and of these by far the most important was sunshine. The sunshine curve and the weight curve, he stated, ran parallel.

Stub-Christisen on the other hand, averred it was a question of nutrition. He considered that the/

the relative deficiency in the vitamin content of the diet towards the end of the winter was responsible for these changes in weight. The more important parallelism he maintained, lay between the potato curve and the weight curve.

Lunde, Pai and Fridmodt-Müller upheld a third theory. In their view the most important factor was the relative humidity of the atmosphere. They advanced evidence to show that the increase in weight was most rapid when there was a high relative humidity, and slower when the relative humidity was low. They believed the explanation to be closely concerned with water retention.

In the discussion which follows this work the theory of seasonal change will be examined further.

Criticism of Previous Investigations.- It may seem rather presumptuous of the present writer with the relatively small amount of clinical material at his disposal, to offer further observation upon a subject which has been so extensively investigated. But the methods previously adopted abounded in fallacies. It required little originality to enumerate the following pitfalls. Some indeed, were noted by the writers themselves, but none of the difficulties were satisfactorily eliminated by them.

Almost all previous authors have based their observations on calculations relating to all the/

the patients in the various sanatoria. But it should be emphasised that fluctuations in the number of patients admitted per month lead to unreliable results. It is well known that in the month or two immediately following admission the majority of patients gain very considerably in weight, and an error in favour of the time of year during which admissions are most frequent (commonly the spring) will be encountered. Contrariwise, where an unusually large proportion of patients have been resident in a sanatorium for a long time, the average gain in weight is comparatively slight, and a false effect may again be attributed to a certain season of the year. The classification of results into positive and negative weeks according to whether the average tendency was to gain or to lose weight, which method was adopted by Fridmodt-Müller, was particularly open to these objections.

Again, where gradual wasting is cut short by artificial pneumothorax, or by any of the other methods with which modern treatment sometimes achieves dramatic results, no indication of the seasonal effect on the weight is detectable. On the other hand, the effects of untoward accidents and complications require to be eliminated. The causes of loss in weight in tuberculosis which bear no relationship to seasonal influences are many. But it is erroneous to expect that, given time, these favourable and unfavourable tendencies will cancel out and leave the/

the general trend unaltered.

The metabolic instability, so common in tuberculosis, adds yet another difficulty. In many patients remarkable fluctuations in weight occur from day to day, and from week to week. In estimating seasonal change it is desirable, therefore, to have readings recorded as frequently as possible. When the weight is registered at monthly intervals it is scarcely possible that a single reading represents the average weight for the month. It would appear that the investigations of Philips, and of Pai, which were based on this method might be unreliable.

Doubtless Strandgaard had all these points in view when he adopted the following method of estimating seasonal variation in the weight of tuberculous persons. In order to calculate the gain or loss in weight for each month, he added the figure for the month to that of the month before and the month after, and then divided the result by three. This practice of smoothing out errors by the "method of moving averages" is not properly applicable to the present problem. In the first place, the monthly values at the beginning and end of the period of observation cannot be treated in this way, and secondly, the curvature which is the essential feature of the observation, becomes flattened when subjected to this process. The method will therefore tend to diminish the seasonal change it was meant to demonstrate.

Notwithstanding these possible defects, the results of the above noted authors were all in approximate agreement. The general trend was to gain weight at all times of year, but more slowly in the spring. A solitary dissentient was Stallybrass (1928) who briefly described the experience gained at Abergele Sanatorium, Denbighshire. There occurred a definite fall in weight in the spring months, followed by a rapid rise in the autumn, up to and even beyond the previous winter level. No details of method were given, but the result will be seen to be more in accord with the writer's findings than those of the other investigators.

The last point to be noted in this review, is that the results of previous workers have not been compared with the normal figures for healthy people. As unfortunately, there appears to be no extensive information available regarding the fluctuation in weight of healthy adults throughout the year, the only well established data are for children, but it is possible that certain inferences in relation to the adult may be made from this, and other evidence bearing on the subject.

The Present Investigation; Selection of Cases.-

In the present study the writer approached the problem along new lines. Only those patients were/

were considered to be suitable for the inquiry who fulfilled the following conditions.-

(1) The weight of each patient was to be observed weekly for at least one complete year.

(2) Each patient was to be in residence in Southfield Sanatorium Colony for a minimum period of two months before the observation was begun, in order to eliminate errors due to excessive gains in weight during the early weeks of treatment.

(3) Patients who were the subjects of collapse therapy were excluded from the scope of this inquiry until six months after the treatment was begun.

(4) This investigation has not incorporated any details relating to patients in whom severe disturbance was noted due to some extraneous cause or accident, and clearly not associable with seasonal influences (see page 80).

The number of patients fulfilling the above conditions was 170. Two patients did so for four years, six patients for three years, and ten patients for two years. In all, therefore, weight records for 198 completed years were available for analysis.

The amount of clinical material on which this inquiry is based was less than that employed in the previous part of this work (on seasonal disturbance in body temperature) for two reasons. Firstly, the period of residence required was greater, and secondly, many cases of bone and joint tuberculosis were/

were immobilised, and weight records were not available for the entire period of treatment.

Calculation of Results.- The method employed in calculating the results was as follows: The weight at the beginning of the period of observation was noted in each patient, and the gain or loss determined for each week of the year from a study of the case records. By summation the total weekly increment or decrement for the whole group was calculated, and by division the average gain or loss per patient for the whole year. In all cases the weight was taken to the nearest quarter of a pound.

Presentation of Results.- The results of the inquiry will be considered under the following headings:

- (1) Seasonal Variation in the Weight of Adult Patients.
- (2) Comparison of the Seasonal Variation in the Weight of Adult Male and Female Patients.
- (3) Cases Exhibiting No Seasonal Variation in Weight.
- (4) The Relationship of the Degree of Systemic Intoxication to Seasonal Variation in Weight.
- (5) Seasonal Variation in the Weight of Tuberculous Children.
- (6) Comparison of the Seasonal Variation in Weight/

Weight Observed in Tuberculous Subjects and in Normal People.

(1) Seasonal Variation in the Weight of Adult Tuberculous Patients.- In the adult group of patients 93 years of weight records were available for analysis. The data were derived from a study of 78 cases of which six were observed for two years, three for three years, and one for four years. The weight curve for the group is illustrated in Figure 15. The average weight for the first week in January (indicated by the point 0 on the ordinate) was 9 stones, 8 pounds.

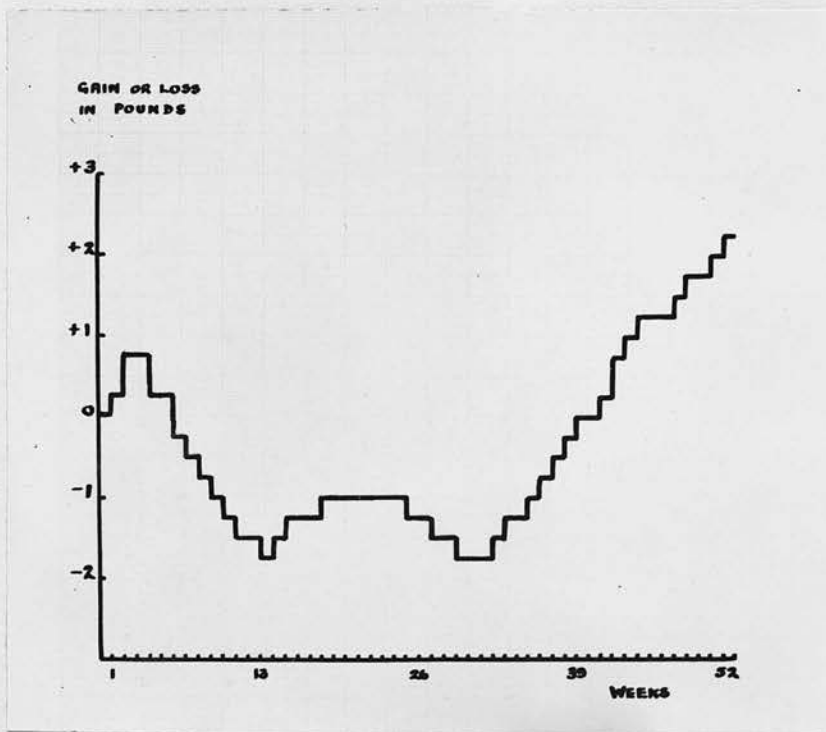


Figure 15.- The average weekly increment or decrement of weight in 78 tuberculous patients. The weight records employed in the construction of this diagram represent a period of 93 years.

Reference to Figure 15 shows that after a very slight gain in weight in January, a steady decline began which continued until the end of March. The average loss of weight during this period amounted to $2\frac{1}{2}$ pounds. From April to the beginning of August only slight variations in weight were observable, but during the last five months of the year the gain in weight was steady and progressive. Since the majority of these patients improved as a result of treatment, their weight was greater at the end of the period of observation than at the beginning.

It should be pointed out that individual patients almost all exhibited a more striking curve than that represented in Figure 15. But whilst some began to lose weight in January, others maintained their winter weight till February, March and even, in a few instances, till April before the decline commenced. Hence, the curve representing the mean of all these variations became definitely flattened in its general conformation.

(2) Comparison of the Seasonal Variation in the Weight of Adult Male and Female Patients.- Of the 93 years of weight records which were furnished by the group of adult patients, 49 were obtained from the records of male cases, and 44 from females. The actual number of male cases was 39, of which three were followed for two years, two for three years, /

years, and one for four years. There were also 39 female cases of which three were observed for two years, and one for three years. Figures 16 and 17 illustrate the variation in weight in these two groups. In the first week of January the average

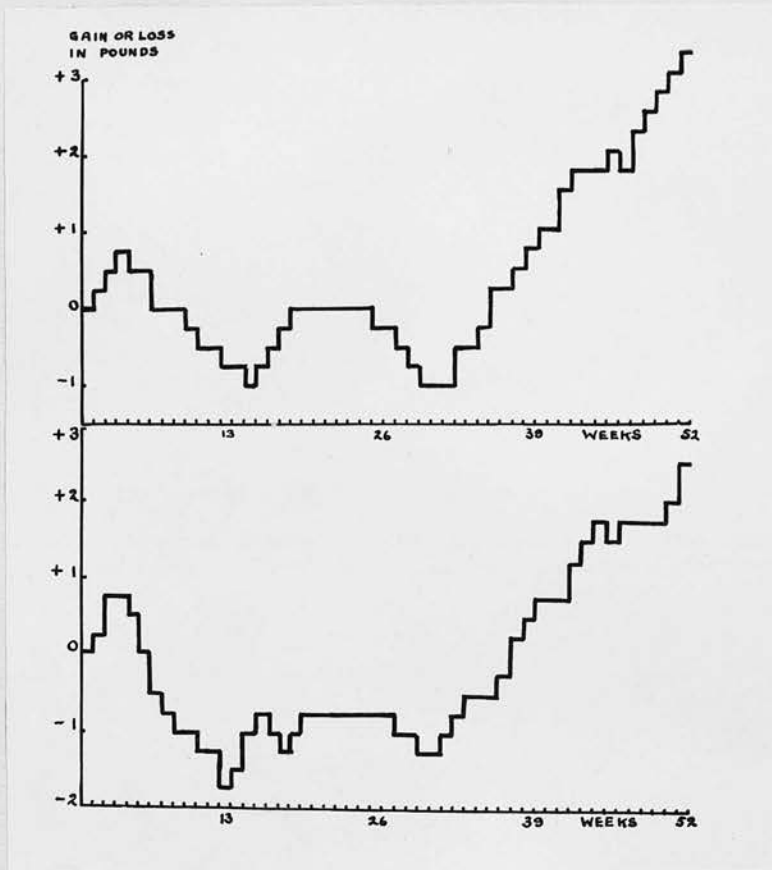


Figure 16: (Upper Curve).- The average weekly increment or decrement in weight in 39 adult tuberculous male patients. (49 years of weight records.)

Figure 17: (Lower Curve).- The average weekly increment or decrement in weight in 39 adult tuberculous female patients. (44 years of weight records.)

weight of the male cases (represented by the point 0 on the ordinate in Figure 16) was 10 stones, $8\frac{1}{2}$ pounds. Likewise, the average initial weight of the female patients (represented by the point 0 on the/

the ordinate in Figure 17) was 8 stones, $8\frac{3}{4}$ pounds. In the subsequent weight curves during the year two points of difference between the sexes were noted. Firstly, the decline in weight in the women patients during the months of February and March, was greater than that registered for the men. The absolute decline in weight was $1\frac{3}{4}$ pounds in the male group of patients and $2\frac{1}{2}$ pounds in the female group. This is not a very marked difference, but if allowance is made for the fact that the average weight of the women patients was almost 2 stones, or 20 per cent., lighter than that of the men, the proportionate difference between the two sexes becomes correspondingly greater. Secondly, whereas the diminution in weight in the male patients during the months of February and March was a gradual process, the corresponding change in the female cases was very much more abrupt. It would appear therefore, that there is some reason for believing that the female sex is somewhat more susceptible to seasonal variation in weight than the male sex.

(3) Cases Exhibiting No Seasonal Variation in

Weight.- Certain classes of patients exhibited no apparent seasonal variation in weight. These were, for example, persons losing ground steadily, and those making excellent progress. There was not a great many of these patients in this investigation for few/

few of either class remain in sanatorium residence for a period of 14 months.

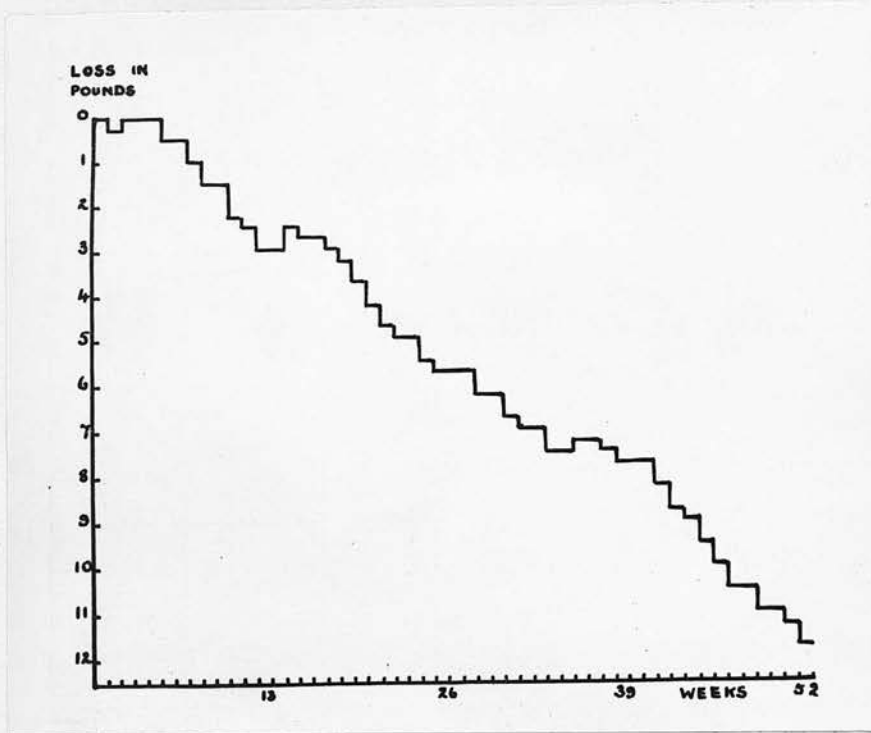


Figure 18.- The average weekly increment or decrement in weight in 12 tuberculous patients who were the subjects of excessive intoxication.

Figure 18 illustrates the weight curve for 12 patients in whom the systemic factor was pronounced, and who were steadily losing ground. The average weight for the first week in January (indicated by the point 0 on the ordinate in Figure 18) was 9 stones, 13 pounds. During the year a steady decline ensued until December when the average weight was 9 stones, 1 pound. But it will be observed that no seasonal fluctuation was apparent in the weight of this small group of cases.

The second group of patients in whom no seasonal variation in the weight was observable comprised those who were gaining weight with unusual rapidity. In none of these patients was the systemic disturbance at all persistent. The average gain or loss for the year is illustrated in Figure 19.

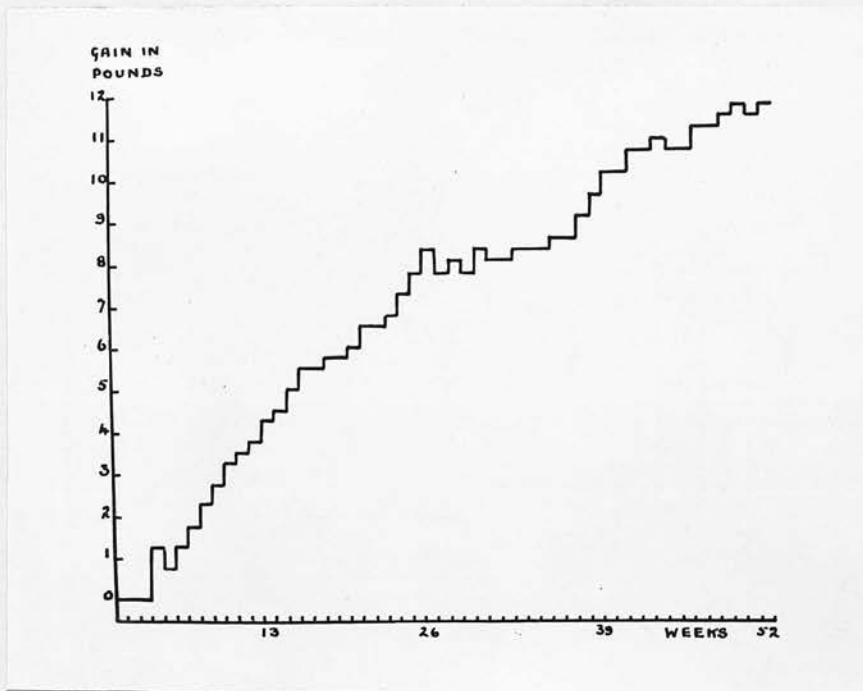


Figure 19.- The average weekly increment or decrement in weight in 8 tuberculous patients who were making unusually rapid progress.

The average weight in this group of patients for the first week in January (indicated by the point 0 on the ordinate in Figure 19,) was 11 stones, 8 pounds, and during the year the gain amounted to 13 pounds. The increase, however, was a fairly steady one, and no seasonal tendency was noticeable.

It may be stated therefore, that when tuberculous/

tuberculous patients gain or lose weight with unusual rapidity, the seasonal variation in body weight disappears, although it is readily observable in the majority of patients who remain in sanatorium residence for a complete year.

Mention was made above (page 72), that no case was included in this inquiry in which there was sudden disturbance due to some known cause which was not associated with seasonal influences. For instance, it was felt that unreliable results would have followed the incorporation of such cases as are illustrated in Figures 20 and 21.

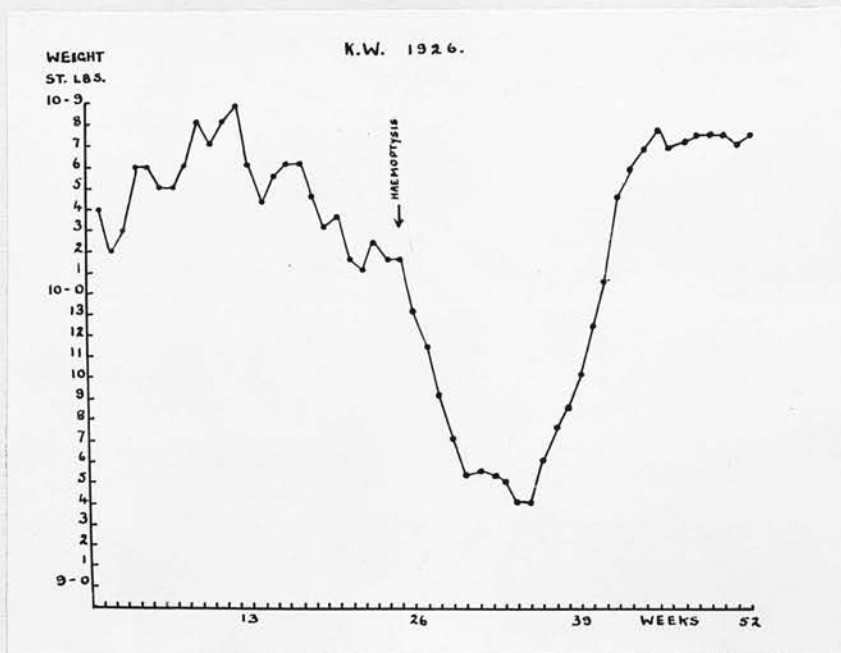


Figure 20.- K.W., 1926. Weight curve for one year showing marked decline in weight following an haemoptysis.

The patient (K.W.) whose weight is described in Figure 20, exhibited a gain in weight during the/

the first quarter of the year, followed by a decline in April and May. But this tendency was grossly exaggerated following an haemoptysis in the month of June. The lowest point was reached in August, and during the autumn rapid recovery took place.

Figure 21 illustrates a remarkable decline in weight in a patient (R.G.) who developed severe renal

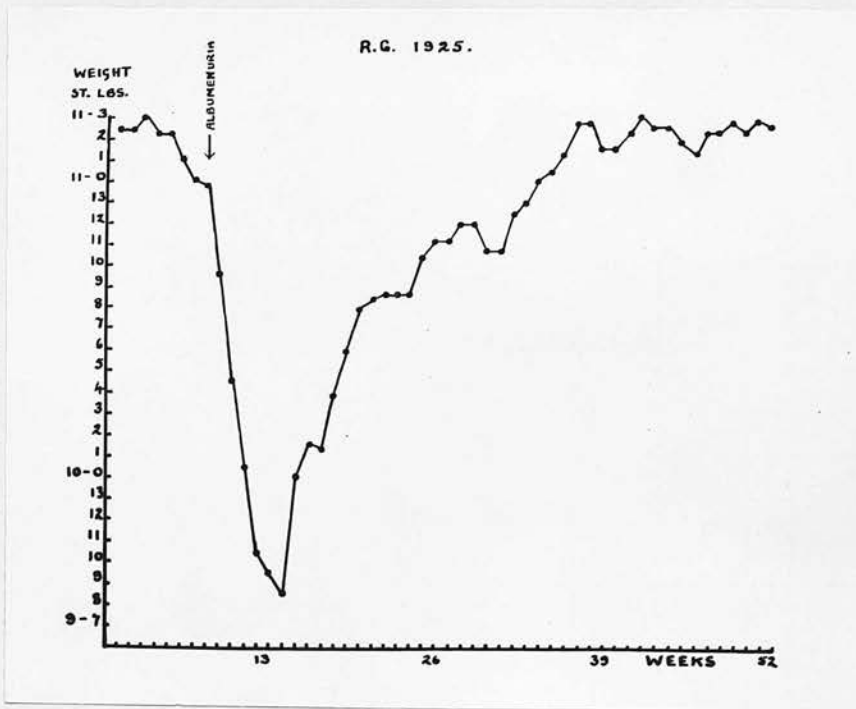


Figure 21.- R.G., 1925. Weight curve for one year showing marked decline in weight following severe albuminuria.

disturbance during a course of sanocrysin therapy. The actual loss of weight in this case amounted to 19 pounds during the spring of the year. Manifestly it would have been undesirable to include the/

the consequences of such untoward events in work designed to discover variations in weight due to more subtle causes.

(4) The Relationship of the Degree of Systemic Intoxication to Seasonal Variation in Weight.- The rules which were formulated on page 72 regarding the choice of cases for analysis in this inquiry made it necessary for each patient selected to be under observation for a period of 14 months. The majority of these cases were the subjects of moderate degrees of systemic intoxication. They constituted the main group of cases and exhibited definite seasonal variation in weight. No such change was noted in the small group of cases in which there was excessive intoxication, nor in the group exhibiting only transient systemic upset. There appeared to be therefore, a possible relationship between the degree of systemic disturbance in tuberculosis and the seasonal variation in body weight. It was considered advisable to investigate this relationship further.

In this connection it is proposed first of all to draw attention to certain cases which were observed for two or more years, and in which the diminishing systemic factor throughout this period could be compared with the seasonal change in weight.

Secondly, consideration will be given to a group of patients in whom the systemic factor was of short/

short duration, and who, though not treated for so long a period as 14 months, were nevertheless under observation during the critical period of the year, namely the spring.

(a) Cases Observed for Two or More Years.- The following case notes and weight curves illustrate the seasonal fluctuations which occurred in the body weight in five patients who were in sanatorium residence for two or more years.

Case 1, C.C., aet. 24: L₃s : 1929-1931.

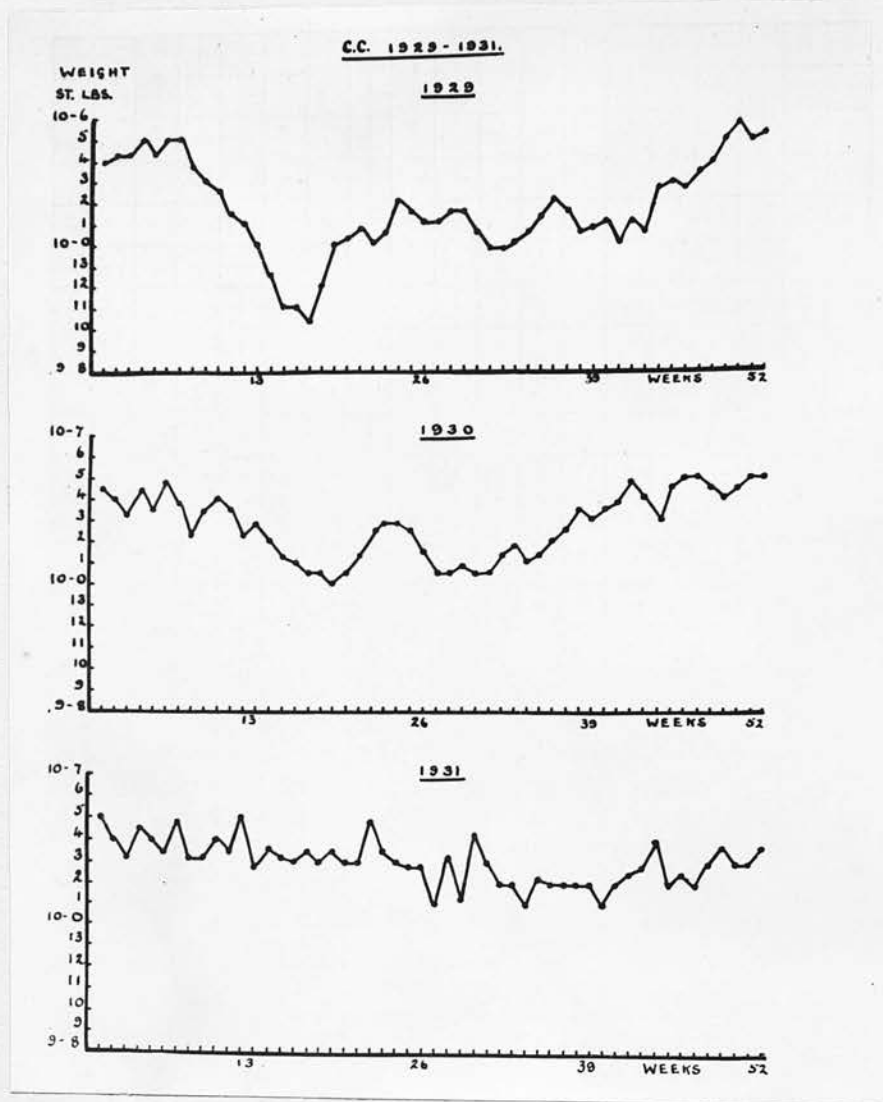


Figure 22.- C.C., 1929-1931. Weight curves for three successive years illustrating diminishing seasonal variation.

Case 1, in which the weight curve for three years is shown in Figure 22, was the subject of a slowly fibrosing lesion which required prolonged treatment to effect complete arrest.

During 1929 there was persistent systemic upset, and as will be seen from Figure 22, a well marked seasonal curve in the body weight was apparent. During the years 1930-1931 disintoxication and cicatrisation were gradually accomplished, and the clinical classification was finally altered to L₃. In 1930 the seasonal change in the weight was less noticeable than in 1929, whilst in 1931 no such trend was to be noted.

Case 2, R.N., aet. 28: L_2s : 1927-1929.

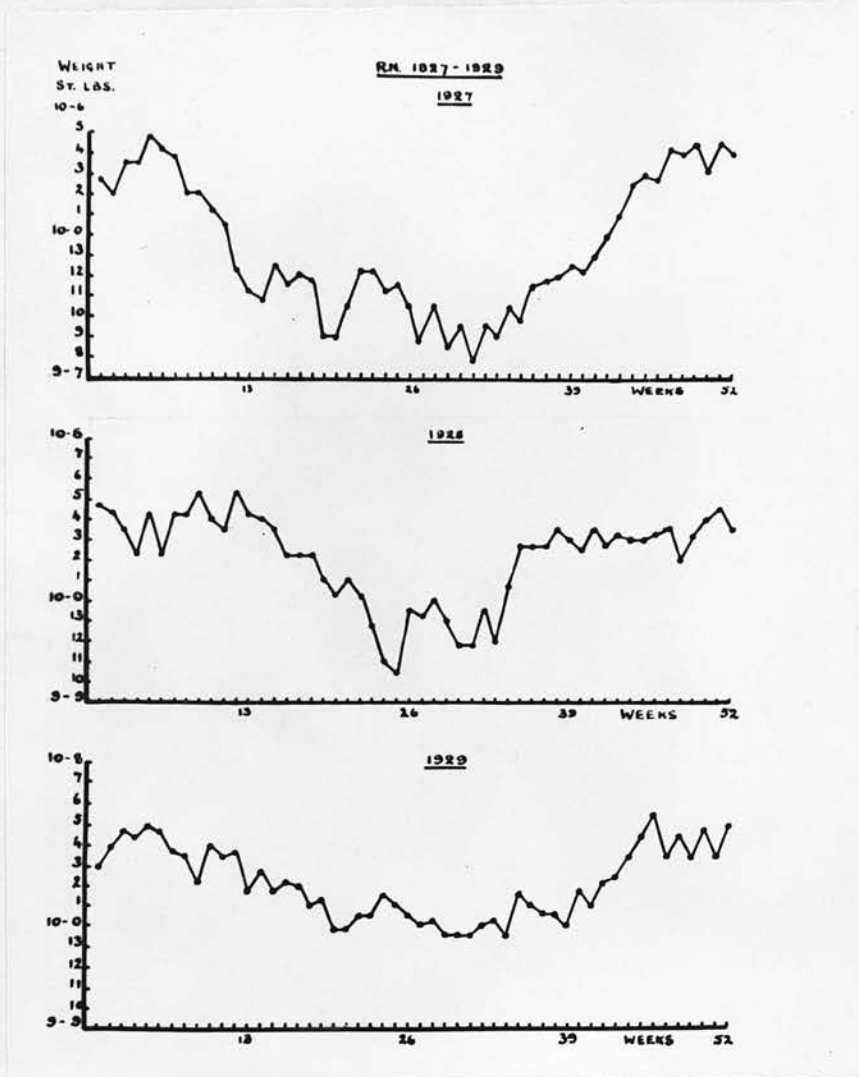


Figure 23.- R.N., 1927-1929. Weight curves for three successive years illustrating diminishing seasonal variation.

This patient presented similar clinical features to those of Case 1, though the local disturbance was somewhat less pronounced.

Figure 23 shows that in the year 1927 a marked seasonal reaction in the body weight was noticeable. The clinical notes for the year indicated that the systemic factor was marked but not excessive at that time. During 1928 and 1929, however, no systemic disturbance was recorded, and it will be observed that during both of these years the seasonal change in body weight was definitely less pronounced.

Case 3, J.L., aet. 17: L₃s : (Lupus). 1923-1925.

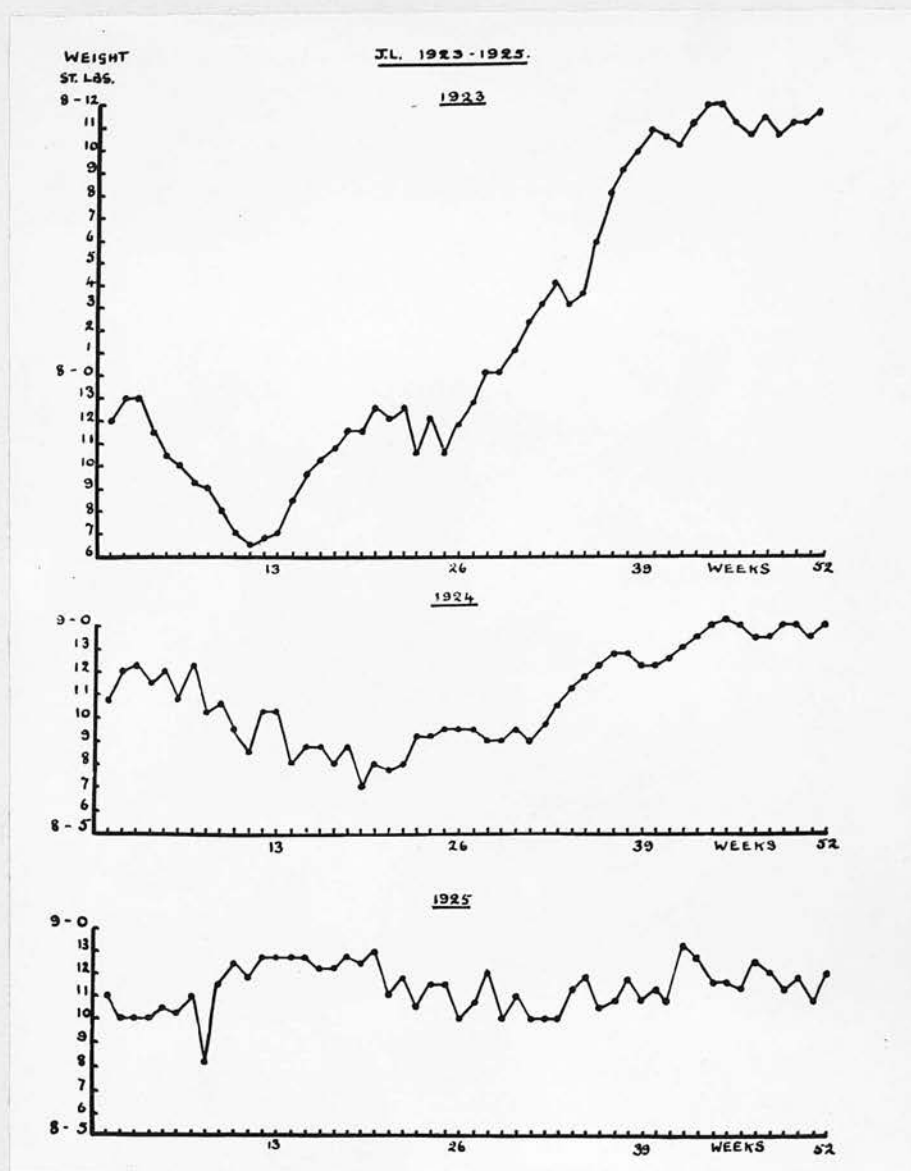


Figure 24.- J.L., 1923-1925. Weight curves for three successive years illustrating diminishing seasonal variation.

As in the two previous cases this patient was in sanatorium residence for three years. The trend of the body weight during this period is illustrated in Figure 24.

During the early part of the year 1923, when the patient was still suffering from some intoxication, there was a typical fall in weight. This was followed by steady recovery till the end of the year when the patient was actually a stone heavier than in January. (The fact that the patient was still growing was largely responsible for this marked increase.)

The/

The year 1924 furnished a rather irregular weight curve, but the gradual decline in the spring and the steady increase during the late summer and early autumn were clearly observable. In 1925, when there was no systemic upset whatever, there was also complete absence of seasonal change in weight.

Case 4, A.G., aet. 29: L₃s : 1924-1925.

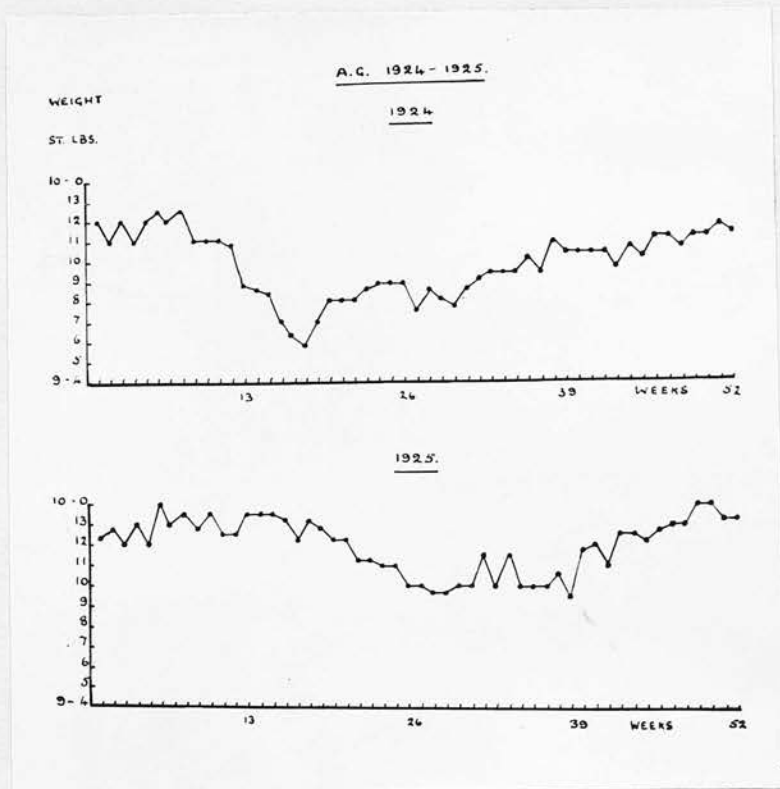


Figure 25.- A.G., 1924-1925. Weight curves for two successive years illustrating diminishing seasonal variation.

This patient was observed for a little over two years. There was slight but persistent systemic disturbance during 1924, and in that year the common spring time diminution in weight was noted. It was followed, however, by a steady recovery during the remainder of the year. But in 1925 when the systemic factor had been eliminated, the weight was maintained throughout the spring, diminished during the summer, and rose to its former level again in the autumn. It should be noted, also, that the decline in weight in 1925 was only half that recorded in 1924.

Case 5, H.H., aet. 20: L₂s : 1923-1924.

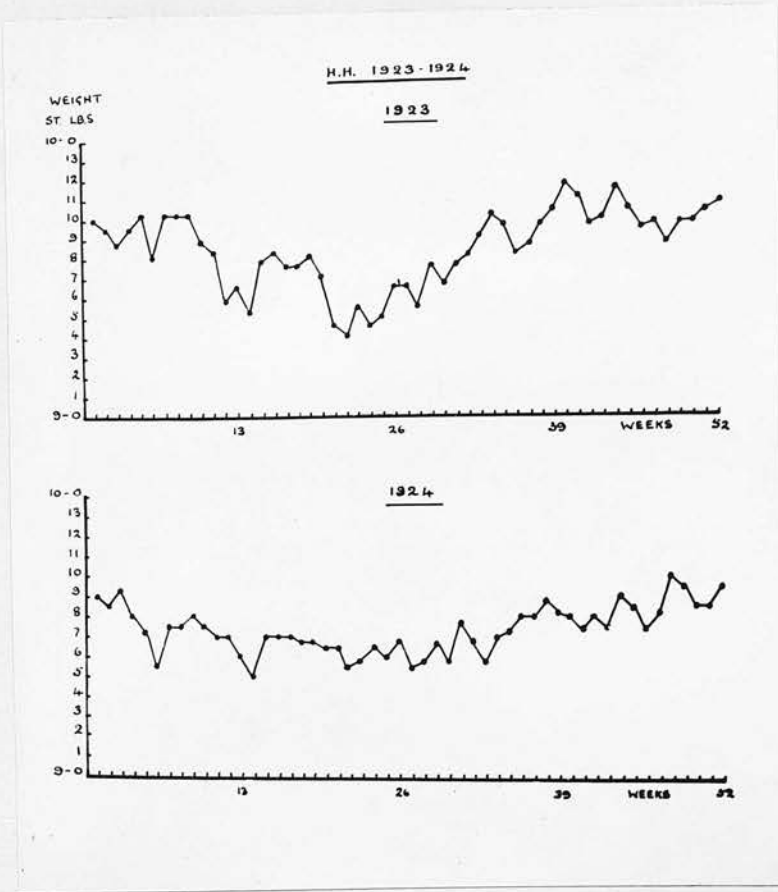


Figure 26.- H.H., 1923-1924. Weight curves for two successive years illustrating diminishing seasonal variation.

The data in this patient, provide weight records which show considerable oscillation from week to week. This in itself was a sign of systemic disturbance and was especially marked during the year 1923. The general trend, however, still demonstrated a diminution in weight during the spring of that year, followed by a recovery during the summer and autumn. In 1924, when no systemic disturbance was registered, both the seasonal variation and the minor fluctuations from week to week were almost entirely eliminated.

Summary of Cases 1 to 5.- A consideration of the data emerging from the records of the above five/

five patients who were observed continuously for two to three years, indicates that the seasonal fluctuation in the body weight is well marked when the patient shows signs of slight or moderate intoxication, but, that as disintoxication proceeds the seasonal change in body weight becomes relatively slight or absent.

(b) Patients Observed During the Spring.- It has already been noted that the 78 adult patients who were selected for this inquiry were the subjects of slight but persistent systemic disturbance necessitating prolonged treatment. But the majority of patients made rapid progress, and were not treated for such long periods as those noted above. It is already clear, however, from the evidence which has been presented in this work, that the months of February, March and April constitute a danger period in tuberculosis, and it was decided to construct a weight curve for these milder cases which, though not resident for a complete year, were under observation during the critical period.

In selecting these milder cases the rules which were formulated on page 72 relating to the duration of treatment were amended to read as follows.-

(1) The weight of each patient was to be observed weekly from the first week in January to the second week in June.

(2) Each patient was to be in residence for a/

a minimum period of two months before the observation was begun.

The number of patients fulfilling these conditions was 37. The average gain or loss in weight during the period of observation is illustrated in Figure 27. The average weight for the first week in January

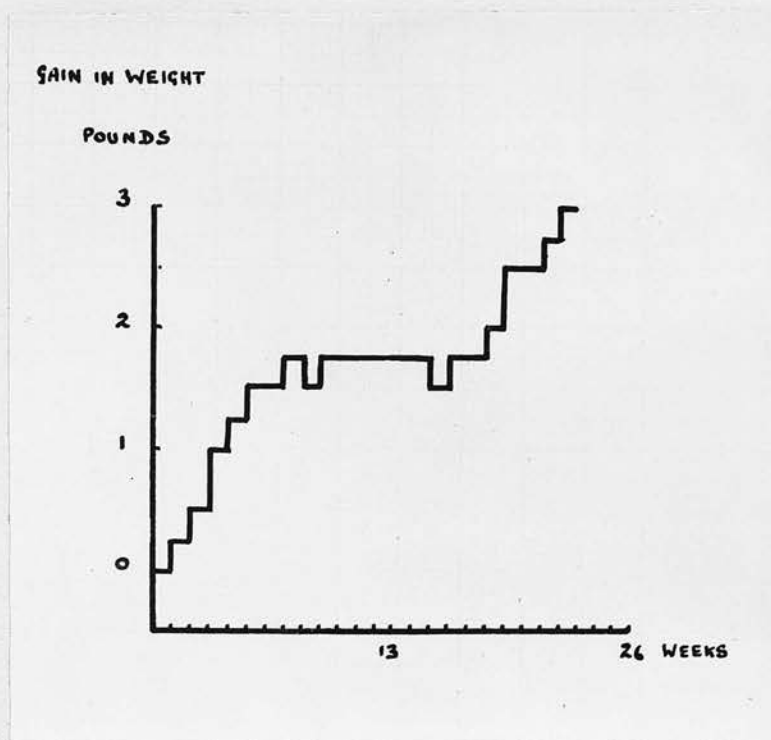


Figure 27.- The average weekly increment or decrement in weight in 37 adult tuberculous patients who were under observation from January to June.

(indicated by the point 0 on the ordinate) was 9 stones, 4 pounds. It will be noted that there was an increase in weight during the early weeks of the year, but that during the months of February, March and April this increase was interrupted. The weight remained at approximately the same level until the/

the end of April. During the remainder of the period of observation, extending from May till the middle of June, the gain in weight was re-established. Thus, even in tuberculous patients with slight and transient systemic disturbance the effect of the danger period of the year on the body weight was apparent.

The Relationship of Systemic Intoxication to Seasonal Variation in Weight: Summary.- The available evidence would seem to show that in tuberculosis there is a relationship between the degree of systemic intoxication and seasonal variation in body weight. This relationship may be summarised as follows:

(i) If the systemic factor is so pronounced as to cause rapid wasting no seasonal change in weight is likely to be observable. (ii) In cases where the toxæmia is slight but persistent, a well defined diminution in weight is apparent during February, March and April, and is followed by a steady increase in the autumn and winter. (iii) When such cases are observed for more than one year, this decline in weight during the spring becomes less pronounced as the systemic factor diminishes. (iv) In milder cases, in which the systemic upset is transient, there is no decline in weight during the spring, but the gain in weight which is usually noted in these patients, is temporarily interrupted. (v) In patients in whom the systemic factor is absent and the increase in weight very rapid, no seasonal trend is apparent.

(5) Seasonal Variation in the Weight of Tuberculous Children.- Eighty-five years of weight records were employed in describing seasonal variation in the weight of tuberculous children. There were 72 cases of which four were observed for two years, three for three years, and one for four years. The age of the patients ranged from $2\frac{1}{2}$ to 11 years, the average being 6 years, 10 months. The weight curve is illustrated in Figure 28. The average weight at the beginning of

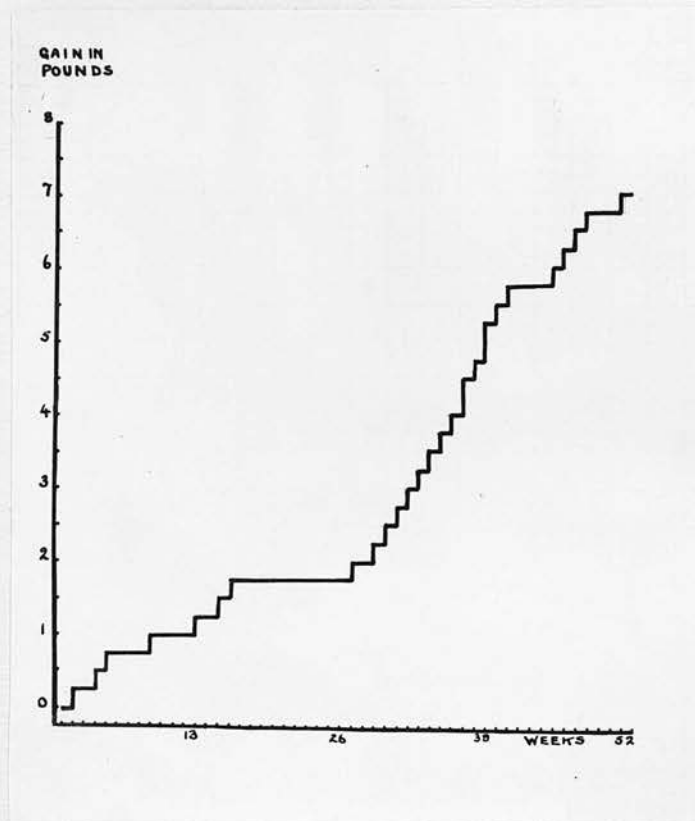


Figure 28.- The average weekly increment or decrement of weight in 72 tuberculous children. The weight records employed in the construction of this diagram represent a period of 85 years.

the year was 3 stones, 2 pounds, and is indicated by the point 0 on the ordinate. During the first six/

six weeks of the year the gain in weight was steady, but from the latter part of February till the beginning of July there ensued a period of comparatively slow growth. During the late summer and autumn a very favourable period followed, which was characterised by more continuous growth than at any other time. This process was retarded, but still marked, during the last quarter of the year.

The seasonal variation in the weight of tuberculous children, as described above, presented certain features in common with that of the adult, if allowance were made for the natural growth of the young subject. The gain in weight during the early weeks of the year was noticeable in both, though more pronounced in the child. During the spring and summer the increase was retarded in the growing child, whilst in the adult there was actually a decline in weight in the spring. But in the late summer and throughout the autumn both groups of patients gained weight rapidly, though this tendency, especially in the children, was less in evidence towards the end of the year.

There were unfortunately insufficient female cases to allow the children to be considered by sexes.

(6) Comparison of the Seasonal Changes in the Weight of Tuberculous Subjects with those Occurring in Normal People: (a) Children.- It is necessary to consider this comparison in relation to children first because it is only for them that definite information has been recorded. The available evidence, however, is conflicting. In America, Emerson (1927) maintained that there was no seasonal variation in the weight of the normal child. In this he agreed with Veeder and Rohlfing (1927) who believed that such changes only began after puberty. On the other hand, Porter (1920) described a slight loss of weight in the spring months, and in 1927 concluded (in co-authorship with Baird) that the period from January to June was one of slow growth in weight, whilst the last six months of the year constituted a period of rapid growth. This was in agreement with Palmer (1933) who has conducted the most exhaustive of the American investigations.

In this country Sir J.B. Orr and H.M. Clark (1930) observed the seasonal trends in the growth in height and weight of 657 school children. Measurements were taken four times in the course of a year. The authors found that the maximum increase in height occurred in the first quarter of the year, and that the maximum increase in weight occurred in the third quarter of the year. This increase was continued, though less rapidly, during the fourth quarter of the/

the year.

Compared with the group of sanatorium cases described above, the normal children gained less weight during the year, but in point of time no difference was observable in the cycle of variation associated with the passing seasons.

(b) Adults.— The comparison of the seasonal variation in weight between normal and tuberculous adults is necessarily largely conjecture owing to the lack of authentic information on changes in the weight of healthy adults throughout the year. But in the absence of more extensive investigation the observations of Pucher and others (1928) may be noted. They found that the weight in five normal subjects was greatest in January and February. They observed a slight decline during the spring, and the minimum point was obtained in July. During the autumn an increase in weight was again observable. The metric system was employed, but the translation of the results into imperial weights showed that the whole variation during the year amounted to $2\frac{1}{2}$ pounds. It will be recalled, however, that $2\frac{1}{2}$ pounds was the average diminution in weight noted by the writer in 78 adult tuberculous patients during the months of February, March and April. The subsequent autumnal increase was somewhat greater as a result of improvement during sanatorium treatment. It is unfortunate/

unfortunate that the above statement on normal people is based on results derived from five individuals only, but the few extensive investigations on the subject known to the writer, have not been available for reference.* As far as is known, therefore, the seasonal variation in the weight of the adult tuberculous subject is very similar to that observed in the normal person.

This supposition is supported by the following considerations. Firstly, the seasonal changes in the weight of tuberculous children were the same as those authoritatively stated to occur in normal children. Secondly, the fundamental change occurring in the body weight of tuberculous patients was noted to be the same in both adults and children. Therefore, the seasonal variation in the weight of adult tuberculous subjects was closely related to the tendency, probably present, but of which there is only inconclusive evidence available in normal people. The above hypothesis becomes still more tenable on recalling the observation made on five patients who were followed for two complete years or more. When the tuberculous process was active the seasonal variation in the body weight was more marked than usual. But when the/

* H. Adersen of Copenhagen (1921, 1923, 1924, 1925) has published observations on "The Physiological Year" and on "Periodical Variations in the Body Weight", but the only copy of his work in this country is in the library of the British Museum.

the stage of complete disintoxication was reached the seasonal variation was slight or even absent.

The seasonal change observed in the adult, therefore, was probably a representation of a physiological tendency, liable to be exaggerated by systemic disturbance.

Conclusions.-

(1) There is a definite seasonal variation in the body weight of tuberculous patients. In adults a decline in weight occurs during February, March and April. The weight remains low during the summer, and rises steadily during the autumn to the maximum in winter.

(2) The adult tuberculous female patient is rather more susceptible to seasonal change in weight than the adult male patient.

(3) In children the seasonal variation is reflected in slow growth in weight during the first half of the year, followed by a much more rapid increase during the second half of the year. The most favourable three months, however, are July, August and September.

(4) The extent of seasonal variation in weight in tuberculosis is related to the degree of systemic intoxication.

(5) Unless exaggerated by the systemic factor the seasonal variation in the weight of tuberculous/

tuberculous patients resembles that noted in normal people.

SEASONAL VARIATION IN THE REACTION TO TUBERCULIN

Introduction.- Of late years numerous inquiries have been made concerning the factors which govern the sensitiveness of the infected animal to the products of the tubercle bacillus. Some circumstances tend to increase this sensitiveness and others to depress it. Having regard to the variety of ways in which the seasons seem to exert an influence on tuberculosis, it was considered possible that the response to tuberculin might also be affected.

Hamburger (1920) has suggested that such a change in the tuberculin reaction does indeed occur. Basing his opinion on clinical observations he stated that a larger number of patients were noted to react positively in the spring than at other times of year. Very little information was given as to how this conclusion was reached. The report was only a preliminary one, and does not seem to have been followed by more detailed investigations. The present inquiry was therefore undertaken in an endeavour to furnish conclusive evidence on the subject.

The Reaction to Tuberculin: General Observations.- In order to assess as accurately as possible the degree of sensitisation to tuberculin at different times of year, it is necessary to collect observations on some indication of tuberculin allergy which/

which is capable of definite measurement.

The reaction to tuberculin is said to be three-fold consisting of signs and symptoms attributable to local, focal and general changes. It is probable that if one of these three allergic manifestations presents a seasonal relationship, all will do so, but the phenomenon most worthy of investigation is that which can be measured with the greatest nicety. In the following pages therefore "Tuberculin Reaction" refers to the local response. By measuring this reaction at different times of year any change in the degree of sensitisation may be determined.

There are, however, three important ways in which tuberculin may be employed in order to elicit a local reaction. These are the cutaneous, per-cutaneous and intra-cutaneous methods. It is not necessary here to enter into a discussion as to the relative merits of these different procedures. For present purposes three essential conditions were required of the method to be adopted, namely, the least possible degree of trauma, complete accuracy of dosage, and economy of tuberculin. (The last point was important for, as will be seen in describing technique, it was necessary to employ the same batch of tuberculin throughout a prolonged series of experiments). To fulfil these requirements it was considered advisable to adopt the intra-cutaneous test.

Criteria of Variation in the Tuberculin Reaction-

In examining the local reaction to tuberculin in successive tests over a given period, it is possible to define two types of variation. Firstly, the intensity of the response may differ from time to time, and secondly the rapidity with which it becomes apparent may vary.

In regard to the first of these points it should be noted that the intensity of the reaction is estimated by measuring the size of an area of erythema, with a variable degree of induration, which arises at the site of inoculation and persists for some considerable time. (The formation of vesicle was very uncommon in the dilutions of tuberculin employed in this work, and was not taken into consideration.)

Secondly, the rapidity with which the response to tuberculin becomes apparent may be studied by examining the reaction at intervals. It may be stated that in the majority of instances the maximum area of erythema is attained in 24 hours. Sometimes, however, the reaction does not attain its maximum until after 48 hours. It is interest, therefore, to ascertain whether this proportion of retarded reactions occurs equally at all times of year, or whether they present a seasonal incidence.

Thus, investigations were conducted in order to observe if any seasonal change took place in the intensity, or in the rapidity of the tuberculin reaction.

The statement made above that the maximum area of erythema occurs 24 hours after the application of tuberculin, requires further comment since some authorities consider that the reaction is most intense after 48 hours. But the analysis of 827 cutaneous tests performed at Southfield Sanatorium Colony by six workers independently, at all times of year, and with various batches of tuberculin, showed that in 49.4 per cent. of tests the response was greater after 24 hours than after 48 hours; that 41.3 per cent. of tests elicited reactions equal after 24 hours and after 48 hours; and that 9.3 per cent. of tests gave rise to the maximum response after 48 hours. It is not certain that these proportions are identical with those resulting from the intra-cutaneous tests, but it is very probable that there is no appreciable difference between the two methods.

The reading of tuberculin reactions after 24 hours, however, is not encouraged owing to the presence of transient pseudo-reactions caused by the protein content of the broth from which the tuberculin is prepared, and it is the reading at 48 hours, for example, that is commonly employed in the standardisation of tuberculin. But in order to ascertain precisely the effects of pseudo-reactions in this investigation control tests were performed in every case with a suitable dilution of veal broth (*vide infra*).

(1) Seasonal Variation in the Intensity of the Tuberculin Reaction: Selection of Patients.- This inquiry was based on tuberculin tests performed on 27 children who underwent treatment in Southfield Sanatorium Colony for a period of one year or more between 1932 and 1935. Children were selected because they exhibited, on the whole, a greater degree of allergy than the adult patients, and therefore fluctuations were more readily identifiable. No patients were included in this investigation if a sudden change in the tuberculin reaction occurred due to some known cause, for example, measles or other intercurrent disease. Patients in whom gradual flagging of the response was associated with increasing intoxication were also excluded from the scope of this inquiry.

Technique of Tuberculin Testing.- Intra-cutaneous tuberculin tests were performed on the patients four times a year, namely in the first week of January, April, July and October. The tuberculin employed was known as "H.24A", and was manufactured in the Laboratory of the Royal College of Physicians, Edinburgh. The tuberculin was preserved in quill tubing and a fresh tube was used when each series of tests was made. The dilutions of tuberculin were always prepared on the day on which the tests were performed.

The technique of the inoculation was the same as that usually employed in the intra-cutaneous test, /

test, but the volume of the dilutions injected was 0.15 cc. instead of the more usual quantity, 0.1 cc. This modification was adopted in order to minimise the effects of needle trauma.

Since the clinical material available was comparatively small, single tests were considered to be insufficiently accurate, and in each patient two dilutions of tuberculin were employed in order to obtain more dependable results. After preliminary trial dilutions of 1:10,000 and 1:100,000 were adopted throughout the experiment. In the average degree of sensitiveness encountered the latter dilution was found to give a faint or mild response, whilst the former usually resulted in a well marked reaction from 20 mm. to 40 mm. in diameter. The dilution of tuberculin commonly employed for diagnostic purposes (1:1,000) was not favoured because it frequently resulted in pronounced pigmentation which had not faded completely before the next test was due to be performed. Even with the stronger of the dilutions noted above, however, this prolonged discolouration did not occur. The necessity of avoiding the use of tuberculin in a dilution of 1:1,000 on this account, was unfortunate since it would frequently have given rise to measurable swelling. But the disadvantage of prolonged pigmentation was so great that weaker dilutions were considered to be essential. The same area of skin was never employed for consecutive tests.

The above reactions were performed on the right arm.

Technique of Control Testing.- It was necessary to provide a control to the tuberculin tests in order to avoid inaccuracies caused by pseudo-reactions. Such reactions are due to the protein element of the culture medium employed in the preparation of the tuberculin. Glycerin-veal broth was treated in the same way as in the manufacture of tuberculin. A suitable quantity (400 cc.) was evaporated to one tenth of the original bulk, and preserved in quill tubing. When the tuberculin reactions were performed on the right arm of the patient, a control test was made on the left arm by injecting intra-cutaneously 0.15 cc. of a 1:10,000 dilution of the concentrated broth. In this way any discrepancy between the true tuberculin reaction and that part of the response which is due to the non-specific protein of the broth, could easily be determined. The interpretation of the control test will be described below.

The reactions to both tuberculin and control tests were measured after 24 hours and after 48 hours. In determining the size of the response, both horizontal and vertical diameters were estimated and the mean of the two recorded. In a very few instances no reliable measurement of the reaction could be made.

Analysis of Data.- The above observations were commenced in 1932 and were continued for three years. During this time tuberculin reactions were performed/

performed on 27 children during four seasons of the year. The complete results may be consulted in Appendix III, Table 1, (page 242).

The data obtained were subjected to close inspection in order to ascertain if the reaction to tuberculin presented any seasonal variation in intensity.

A tuberculin test was stated to be positive when an area of erythema, arising at the site of injection, measured at least 8 mm. in diameter after 24 hours and persisted until after 48 hours. A negative reaction was judged to be one in which the response elicited measured less than 8 mm. in diameter.

Mathematical uniformity in the size of successive reactions after intervals of three months could not be expected, and it was decided to ignore small variations in the results. In comparing measurements of consecutive tests, no change in the intensity was regarded as a significant increase or decrease unless a variation of at least 5 mm., or in certain cases of 7 mm., was noted. In cases in which the reaction to the second dilution of tuberculin was small, measuring only 10 mm. or so in diameter, variations were slight and were ignored. But in well marked reactions, which constituted the great majority, the following standards of variation (subject always to the interpretation of the control test to be described below) were considered to represent a real change in the intensity of the reaction, as compared with the/

the previous test.-

(a) An observed increase (or decrease) of at least 5 mm. in the reactions to dilutions 1 and 2, after 24 hours and after 48 hours.

(b) An observed increase (or decrease) of at least 5 mm. in the reaction to dilution 1 after 24 hours and after 48 hours, but not in dilution 2.

(c) An observed increase (or decrease) of at least 5 mm. in the reactions to dilutions 1 and 2, after 24 hours, or after 48 hours, but not after both these intervals.

(d) An observed increase (or decrease) of at least 7 mm. in the reactions to dilution 1, or dilution 2, after 24 hours, or after 48 hours but not after both these intervals.

In the reactions obtained an increase of 5 mm. in diameter represented a relatively pronounced change, and one not likely to be due to experimental error.

The importance of the control test in the analysis of the results requires further attention. For example, if both the control reaction and the tuberculin tests elicited a more pronounced response (i.e. greater by 5 mm. or more) as compared with the readings obtained from tests performed three months previously, no increase in the intensity of the tuberculin reaction during the interval could be inferred. On the other hand, if the control reaction gave results similar to those obtained in a previous test, whilst/

whilst the tuberculin tests evoked a greater response, an increase in the intensity of the latter had probably occurred. Further, if the apparent increase in the tuberculin reaction were observed only after 24 hours but was not significant (i.e. less than 5 mm.) after 48 hours, the increase was nevertheless considered to be a real one if the control reaction had remained constant. Conversely, an increase observed in the tuberculin reaction after 48 hours was deemed to be a real change if no increase in the control reaction had been recorded after 24 hours. (The control reaction was with one exception always negative after 48 hours.)

Results.- When the reactions to tuberculin obtained in the 27 cases which formed the subject of this inquiry, were examined according to the standards enunciated above, it was discovered that only eight cases presented reactions which were unusually pronounced at a certain time of year. Of these eight cases five exhibited increased tuberculin reactions in April, one in January, one in July, and one in October. In the remaining 19 cases no seasonal change in the intensity of the tuberculin reaction was observable. The complete data have been recorded in Appendix III, but the results in two illustrative cases may be seen on reference to Table 11 and the accompanying case notes.

Case 14. D.K.- Five series of observations were/

were carried out in this patient between July, 1933 and July, 1934. It will be noted that the results recorded in January, 1934 represented an increase in the intensity of the tuberculin reaction as compared with the two previous observations. In April, 1934, the response was still more pronounced, whilst in the following July a marked diminution was recorded. These changes were noted both after 24 hours and after 48 hours. Throughout the period of observation only the slightest differences were observable in the control reaction. The indication was, therefore, that in this patient the tuberculin reaction was more pronounced in the month of April than at other times of year.

Table 11.- Diameters of tuberculin reactions at different times of year in two cases illustrating seasonal change in the intensity of the reaction. The figures are in millimetres. (For complete results see Appendix III, Table 1, page 242.)

Case No.	Date of Observation	Readings at 24 hours			Readings at 48 hours		
		D.1	D.2	C	D.1	D.2	C
14 (D.K.)	July 1933	25	14	17	35	22	8
	October 1933	26	17	19	26	17	10
	January 1934	45	25	18	42	23	10
	April 1934	55	30	20	55	25	11
	July 1934	32	20	17	26	19	10
4 (J.G.)	October 1932	19	11	16	20	12	-
	January 1933	16	10	16	19	11	-
	April 1933	27	11	19	20	11	-
	July 1933	20	10	20	19	12	-
	October 1933	17	10	16	17	?	-
	January 1934	19	8	14	21	?	-
	April 1934	28	10	16	20	10	-
	July 1934	20	11	17	17	?	-
	October 1934	19	8	14	21	9	-
	January 1935	17	10	15	20	9	-

D.1 = Dilution 1 of tuberculin.
D.2 = Dilution 2 of tuberculin.
C = Control.

Case 4. J.G..- Ten series of tuberculin tests together with control reactions were performed on this patient between October, 1932 and January, 1935. It will be noted from the results in Table 11 that the reaction to dilution 1 of tuberculin varied between 16 mm. and 20 mm. in diameter on eight of the ten occasions when the tests were performed. But on two occasions, namely April, 1933 and April, 1934, the diameter of the response was recorded as 27 mm. and 28 mm. respectively. In dilution 2 and in the control reaction insignificant fluctuations in the diameters of the reactions were noted. In this patient no evidence of seasonal variation in the tuberculin test was found from readings taken after 48 hours, but since the reactions recorded after 24 hours during April, 1933 and April, 1934 were at least 7 mm. greater than those recorded at other times of year, and since this change was unaccompanied by any corresponding increase in the control reaction, greater intensity of the tuberculin reaction during the spring could be inferred.

Increasing Sensitiveness to Tuberculin Apart from Seasonal Influences..- A brief digression is necessary in order to describe certain interesting results obtained in the course of the above inquiry. It was stated that 19 cases out of the series of 27 exhibited no seasonal change in the intensity of the tuberculin reaction. In some of these cases slight/

slight irregularities in the results were noted, whilst others revealed a remarkable uniformity. But in five cases a phenomenon was observed which requires further attention.

The tuberculin reaction in these five subjects steadily increased in intensity throughout the period of sanatorium treatment. The complete details in these cases are recorded in Appendix III, Table 1, page 242, but the results in an illustrative case may be seen on reference to Table 12.

Table 12.- Diameters of tuberculin reactions in a patient (E.M.) who illustrated a continuous increase in the sensitiveness to tuberculin.

Case No.	Date of Observation	Readings at 24 hours			Readings at 48 hours		
		D.1	D.2	C	D.1	D.2	C
21 (E.M.)	April 1934	31	18	30	26	19	-
	July 1934	38	24	34	36	14	-
	October 1934	42	24	32	48	24	-
	January 1935	48	28	32	46	24	-

D.1 = Dilution 1 of tuberculin.
D.2 = Dilution 2 of tuberculin.
C = Control.

It will be seen from the above table that the reactions to both dilutions of tuberculin, read after 24 hours and after 48 hours, increased steadily in diameter during the period of investigation. In the control tests no increase was noted, and therefore the/

the change was due to greater sensitiveness on the part of the patient to tuberculin.

It is worthy of mention that each of the five patients referred to above, in whom the intensity of the tuberculin reaction increased steadily during the period of observation, made exceedingly good progress. Similar findings have been noted repeatedly in patients who were under observation for a shorter period of time. So far as is known all these patients have maintained good health since discharge from the sanatorium, a fact which suggests that increasing sensitiveness to tuberculin is indicative of good progress.

The relationships of allergy and immunity do not fall within the scope of this work, but the investigation of an augmented reaction to tuberculin as a test of prognosis may be worthy of further study. (Estimations of prognosis based on single tuberculin tests are common but unreliable.)

Summary.- Twenty-seven children suffering from tuberculosis were subjected to the tuberculin test in two dilutions in January, in April, July and October.

Only five of these cases presented reactions which were unusually intense during the month of April, whilst one revealed the maximum response in January, one in July, and one in October.

In 19 cases no seasonal variation in the tuberculin test could be demonstrated.

Conclusion.- There is no evidence to indicate/

indicate that the intensity of the tuberculin reaction is commonly more pronounced during the spring than at other times of year.

(2) Seasonal Variation in the Rapidity of the Reaction to Tuberculin.- It has been stated above that in a certain proportion of cases the tuberculin reaction is found to be more marked after 48 hours than after 24 hours. The object of the second part of this inquiry is to ascertain if there is any seasonal variation in the incidence of early and late reactions.

Selection of Patients.- Initially attention was devoted to the data obtained from 108 series of tuberculin tests performed in the 27 cases which formed the subject of the first part of this investigation. The information gained was later supplemented by the incorporation of additional clinical material.

Analysis of Data.- The readings obtained from the tuberculin tests were closely inspected, devoting special attention to the size of the reactions after 24 hours as compared with the readings after 48 hours. The results were tabulated according as the readings proved the response to be.- (a) greater after 24 hours as compared with the readings at 48 hours, or (b) of equal intensity after 24 hours and 48 hours, or (c) more intense after 48 hours than after 24 hours.

In analysing the results no difference between the readings taken at 24 hours and at 48 hours was considered to be present unless the recorded discrepancy between the two amounted to at least 5 mm. If the results obtained at 24 hours and at 48 hours were equal in respect of dilution 1, but those from dilution 2 presented a discrepancy of 5 mm. or more, the result was based on the effects of the stronger dilution whilst the reaction from the weaker dilution was ignored.

Results.- The results from the above analysis may be studied in Table 13.

Table 13.- The analysis of 108 series of tuberculin tests according to the season of the year and the size of the reaction at stated intervals.

Month	Number of dual tests	Percentage number of tuberculin tests recorded as (a), (b), (c).		
		(a)	(b)	(c)
January	26	53.8	34.6	11.6
April	26	73.1	23.1	3.8
July	26	42.3	46.2	11.5
October	30	33.3	56.6	10.1

- (a) Reactions greater at 24 hours than at 48 hours.
- (b) Reactions equal at 24 hours and at 48 hours.
- (c) Reactions greater at 48 hours than at 24 hours.

Two main facts emerge from a consideration of the data in Table 13. Firstly, the proportion of tuberculin/

tuberculin reactions which were found to be more intense after 24 hours than after 48 hours was greater in April than at other times of year. Secondly, the proportion of reactions which were found to be greater after 48 hours was less during the month of April than at other times of year. It would appear, therefore, that the tuberculin reaction in this series of cases was accelerated during the spring.

It need not be emphasised however that 108 series of tests in 27 patients do not constitute a very extensive inquiry, and in order to test the validity of the results in Table 13 the investigation was extended to incorporate the results in all children undergoing treatment in Southfield Sanatorium Colony between 1932 and 1935, irrespective of the duration of observation in each case. The extended inquiry was now based on 66 patients whilst the number of dual tests performed amounted to 213. Owing to the fact that fewer patients were undergoing treatment during the summer than during the winter, a smaller number of observations was made during the second and third quarters of the year than during the first and fourth.

When the additional data thus made available were added to those previously tabulated, the final analysis emerged as in Table 14. The detailed results may be consulted in Appendix III, Table 2, page 246.

Table 14/

Table 14.- The analysis of 213 series of tuberculin tests according to the season of the year and the size of the reaction at stated intervals.

Month	Number of dual tests	Percentage number of tuberculin tests recorded as (a), (b), (c).		
		(a)	(b)	(c)
January	64	46.8	39.1	14.1
April	48	64.6	31.3	4.1
July	40	42.5	42.5	15.0
October	61	31.1	55.7	13.2

- (a) Reactions greater at 24 hours than at 48 hours.
 (b) Reactions equal at 24 hours and at 48 hours.
 (c) Reactions greater at 48 hours than at 24 hours.

It will be seen from Table 14 that the percentage number of occasions on which the reactions to tuberculin were greatest after 24 hours was 64.6 in the month of April, whilst the proportions for the remaining three periods were 46.8 per cent. in January, 42.5 per cent. in July, and 31.3 per cent. in October. Similarly the percentage number of reactions which did not attain the maximum intensity until after 48 hours was only 4.1 in the month of April, as compared with 14.1 per cent. in January, 15.0 per cent. in July, and 13.2 per cent. in October.

These findings do not provide such a marked contrast between the spring and the rest of the year as was represented in Table 13, but nevertheless the evidence is in favour of an accelerated response to/

to tuberculin in the month of April.

Summary.- Sixty-six patients were tested with tuberculin at different seasons of the year and of these 27 were observed for a complete year. Two hundred and thirteen series of reactions were performed. In the month of April an unusually large proportion of tuberculin tests exhibited the maximum response after 24 hours, whilst an unusually low proportion exhibited the maximum response after 48 hours.

Conclusions: The Intensity of the Reaction to Tuberculin.- There is no reason for believing that the intensity of the tuberculin reaction is commonly increased during the spring, though a few patients exhibit this phenomenon.

The Rapidity of the Reaction to Tuberculin.- The tuberculin reaction appears to be accelerated in the spring, but confirmation of this is desirable.

PART IIISEASONAL VARIATION IN MORTALITY
WITH SPECIAL REFERENCE TO TUBERCULOSIS

Introduction.- The clinical investigation of seasonal variation in tuberculosis cannot in itself be complete. In Parts I and II of this work certain cumulative evidence has been presented which seems to leave little doubt that tuberculosis is a disease which is greatly influenced by the changing seasons. Nevertheless, it is desirable to have confirmation of these observations based on a study of vital statistics. In those cases which end fatally the last incident in the disease is thus recorded, and the seasonal incidence of death can be compared with the changes which were observable in life.

Again, vital statistics may furnish an answer to certain problems which it was not possible to investigate clinically. In the preceding parts of this work, there was insufficient clinical material to determine at what age the tuberculous subject is most susceptible to seasonal influences. By analysing the statistical records an answer to this question may be suggested. In the following pages, therefore, it is proposed to introduce any corroborative or additional information which will be of service in considering/

considering seasonal variation in tuberculosis.

Review of Previous Literature.- Data concerning the seasonal variation in mortality from tuberculosis (all forms) and from pulmonary tuberculosis are scanty. But statistics relating to tuberculous meningitis are not uncommon. In Glasgow, M'Cracken (1933-34) found that the largest proportion of deaths occurred during the month of May, whilst comparatively few were recorded in the late summer and autumn. Since this observation was essentially similar to the experience of other authors it seems unnecessary to describe all the previous publications in detail, but a summary of the more important investigations may be seen on reference to Table 15.

Table 15.- Summary of observations concerning the seasonal incidence of tuberculous meningitis.

Author	Locality	Duration of observation	Maximum mortality	Minimum mortality
(1)	Glasgow	1915-1933	V	X
(2)	Finland	1905-1924	I to VI	IX to XII
(3)	Vienna	1917-1926	III to V	IX to XI
(4)	Italy	(140 cases)	III to IV	X to XII
(5)	Italy	(59 cases)	spring	autumn

- | | |
|-------------------------|----------------------|
| (1) M'Cracken (1933-34) | (4) Simonetti (1928) |
| (2) Ruotsalainen (1925) | (5) Campani (1932) |
| (3) Götzl (1930) | |

Except where otherwise stated the results in Table 15 are based on the statistical returns for the locality of observation. Roman numerals are employed instead of the names of the months.

Two authors have published results relating to military tuberculosis. Campani (1932) observed the occurrence of generalised dissemination in 40 cases, and of these as many as 24 were noted in the spring. Von Pirquet (1930) in analysing the statistics of the English Registrar General for the years 1912 to 1920, came to the conclusion that military spread in tuberculosis was most likely to occur between the tenth and twentieth days of April.

The seasonal variation in the death rate from tuberculosis (all forms) has been investigated in Germany by Möllers (1926). He collected statistics from all towns of more than 15,000 inhabitants. He found that the maximum death rate for the period 1912 to 1925 (excluding the war years) occurred in the months of February, March and April, whilst the lowest death rate was noted from August to November. He also found in a detailed scrutiny of the figures for the largest towns in Germany that the eleventh to the fifteenth weeks of the year were those in which the largest number of deaths were registered.

In an extensive epidemiological study Gottstein (1930) defined the seasonal trend in the mortality from pulmonary tuberculosis. He computed figures/

figures for two German cities, Berlin and Hamburg. The results in these two places differed widely probably due to the fact that whilst the data for the city of Hamburg extended over a period of 50 years (1820 to 1870), those for Berlin were based on the deaths occurring in a single year (1910). It is therefore probable that the results for Hamburg were the more accurate. It was found that the greatest number of deaths from pulmonary tuberculosis occurred in February, March and April, and the fewest in July, August and September.

The last two authors, however, presented their results somewhat differently. Möllers, as has been stated, calculated the death rates for tuberculosis for each calendar month during the period of observation. Gottstein computed the proportion of deaths occurring in each month out of 1,200 fatal cases. The former method gives an excellent survey of the variations that occur in different years, and of the influence of any abnormal factors which may operate from time to time. The latter procedure is of value in comparing different diseases, sexes, or age groups. Both methods will be employed in the present work.

The work of Alexander Buchan (1875) deserves mention since it must be one of the earliest investigations into seasonal variation in disease. He described the seasonal incidence of deaths from pulmonary tuberculosis in London from 1845 to 1874. Basing/

basing his opinion on the weekly returns of registered deaths he stated that very few irregularities occurred from week to week, and that phthisis was a disease in which very little seasonal influence was observable. In "Scrofula" too he found that little seasonal change was noticeable, but in "Tabes mesenterica" a marked seasonal variation occurred with the maximum mortality from July to September. These three findings are difficult to correlate with each other and with those of other writers. There is no apparent reason for markedly different seasonal trends in mortality as between one form of tuberculosis and another, unless it be in errors in diagnosis, or in the registration of deaths. The peak in the mortality from tabes mesenterica in midsummer suggests a possible confusion with diarrhoea and enteritis, whilst the almost entire absence of seasonal variation in fatalities from pulmonary tuberculosis may be due to faulty registration as well as to faulty diagnosis. From the evidence at hand it is not possible to accept this early investigation of Buchan as a reliable indication of seasonal trends in the mortality from tuberculosis.

Plan of the Present Investigation.- The data in the following inquiry refer to seasonal variation in mortality as it occurs in Scotland. The mortality figures were derived from the Annual Reports of/

of the Registrar General together with the Monthly Returns for the Sixteen Principal Towns. Initially, attention was devoted to the decade 1921 to 1930. This period was later extended to incorporate the years 1931 and 1932 whilst the years 1922 and 1929 (in which epidemics of influenza distorted the normal seasonal trend of mortality) were excluded. The results obtained will be presented under the following main headings:

I Seasonal Variation in the Mortality from Tuberculosis.

II Seasonal Variation in the General Mortality and in Selected Causes of Death.

III The Relationship of Age to Seasonal Variation in Mortality.

IV The Relationship of Climate and Meteorology to Seasonal Variation in the Mortality from Tuberculosis.

V Seasonal Variation in Mortality: Summary.

I SEASONAL VARIATION IN THE MORTALITY FROM TUBERCULOSIS

The seasonal variation in the mortality from tuberculosis will be described in relation to all forms of the disease, and to certain different forms of the disease; and in relation to the sexes. Seasonal variation in mortality in different age groups will be treated in a separate section.

A. Seasonal Variation in the Mortality from Tuberculosis (All Forms).- A general review of the mortality from tuberculosis at different times of year was first considered by estimating the death rate for each month of the decade 1921 to 1930. For this purpose it was first necessary to ascertain the "monthly population" of Scotland during this period. These figures were kindly supplied by Mr Alexander McKinlay of New Register House, Edinburgh. The monthly death rate from all forms of tuberculosis and from non-pulmonary tuberculosis was then calculated. The results are recorded in Appendix IV, Table 1, (page 249), and also graphically in Figure 29.

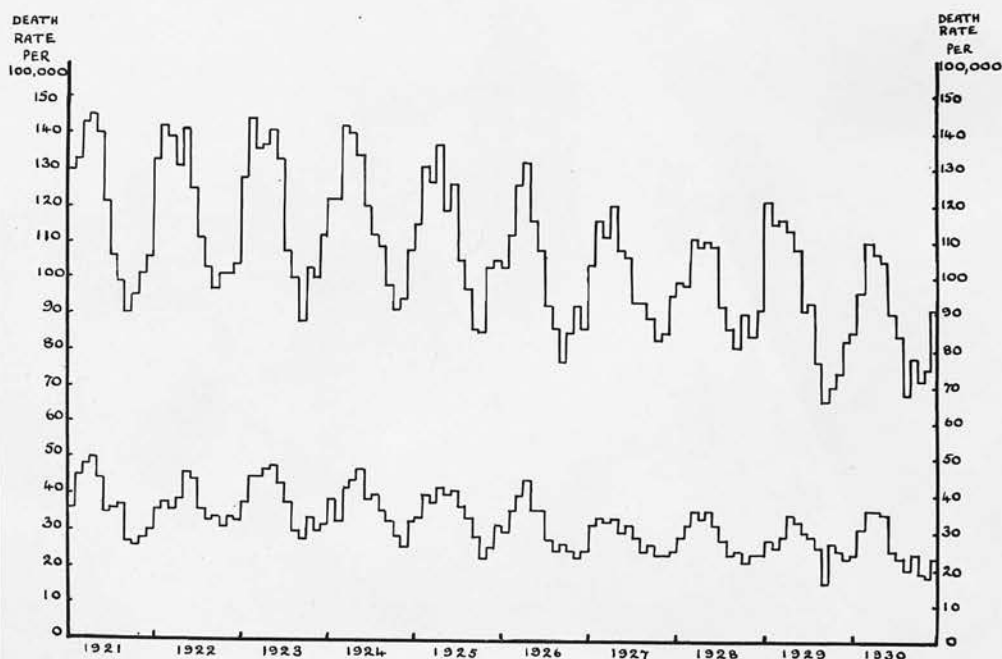


Figure 29.- Scotland, 1921-1930. Monthly death rates from all forms of tuberculosis (upper curve), and from non-pulmonary tuberculosis (lower curve).

In Figure 29 the upper curve represents the mortality rate from all forms of tuberculosis, and the lower curve represents the rate for non-pulmonary tuberculosis. It will be noted that the death rate from all forms of tuberculosis was highest in the months of February, March, April and May, and lowest in September, October and November. Similar findings may be observed in the non-pulmonary forms of the disease.

The year 1929 is interesting on account of the fact that the seasonal change was complicated by a severe epidemic of influenza which occurred in the month of January. This epidemic hastened the death of many patients who otherwise would have died later in the year, and resulted in the greatest fatality rate being recorded in January rather than in the spring. A similar epidemic occurred in the year 1922 when the maximum death rate from tuberculosis (all forms) occurred in February. It should be noted, however, that the normal seasonal variation was encountered among the non-pulmonary cases in both these epidemic years, a fact which will call for further comment.

The average seasonal variation in the deaths from tuberculosis for the whole decade is to be found in Figure 30 which represents the monthly incidence of 1,200 deaths. This figure is based on the convenient mean of 100 deaths per month. The data from which this graph was constructed are to be found in/

in Appendix IV, Table 2, (page 253).

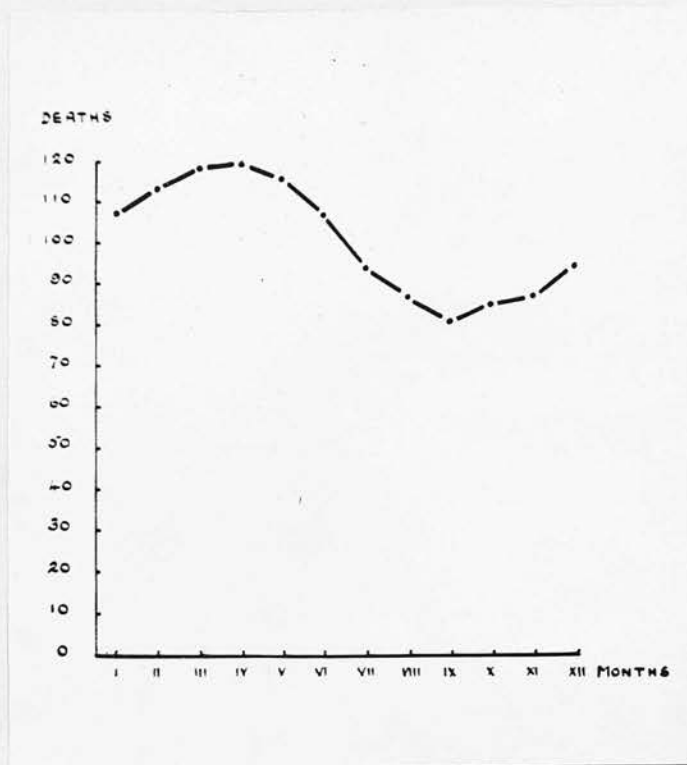


Figure 30.- Scotland, 1921-1930. The monthly distribution of 1,200 deaths from tuberculosis (all forms).

The method of calculating the results in this figure was as follows. The number of deaths from all forms of tuberculosis for each month of the decade is available from the Annual Reports of the Registrar General for Scotland. The number of deaths which would have occurred if all the months had been of equal length was estimated. For this purpose it was supposed that all the months were of 31 days' duration, and the number of deaths in February, April, June, September and November was increased accordingly. The annual total for twelve months of 31 days was arrived at by addition, and thereafter the monthly incidence/

incidence of 1,200 deaths was calculated by simple proportion. This method was adopted for all the curves hereafter.

In studying these graphs two points should be noted, namely, the excursion of the curve above and below the mean of 100 deaths per month, and the time of year at which the maxima and minima were attained.

In Figure 30 it will be observed that the greatest number of deaths from tuberculosis was registered during the months of March, April and May. The smallest number of deaths was notified from August to November. On the basis of 100 deaths per month it will be noted that the maximum point in April was 119, and the minimum point in September was 80, representing a difference of approximately 20 per cent. above and below the mean.

B. Seasonal Variation in the Mortality from Certain Different Forms of Tuberculosis.- The extent to which seasonal variation occurs in the mortality from certain forms of tuberculosis may be seen on reference to Figure 31. In this figure the three curves represent the distribution of 1,200 deaths from pulmonary tuberculosis, from meningeal tuberculosis, and from others forms of the disease during the decade 1921 to 1930. The complete details may be consulted in Appendix IV, Table 3, (page 254).

Pulmonary Tuberculosis.- The seasonal trend/

trend in the mortality from pulmonary tuberculosis attained its maximum in March and its minimum in September. On the basis of 100 deaths per month the maximum figure was 118 and the minimum was 79.

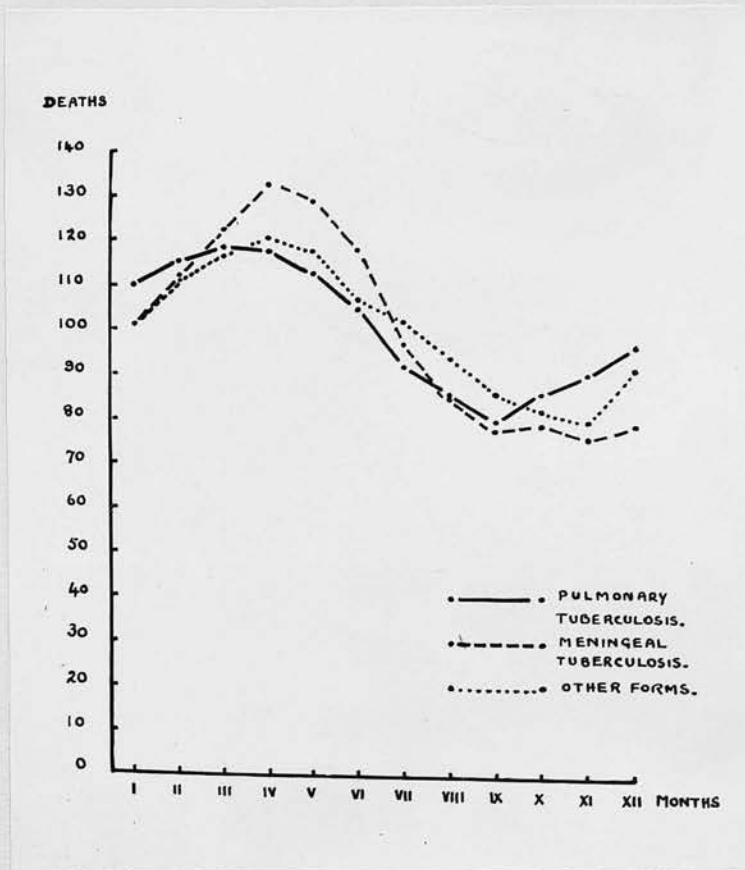


Figure 31.- Scotland, 1921-1930. Monthly distribution of 1,200 deaths from certain forms of tuberculosis.

Meningeal Tuberculosis.- The largest number of deaths from meningeal tuberculosis occurred in April, and the smallest number in November. The excursion of the curve is much greater than in pulmonary tuberculosis, the proportion of 100 deaths per month/

month reaching 132 in April, and falling to 74 in November.

Other Forms of Tuberculosis.- The seasonal variation in mortality from the remaining manifestations of tuberculosis was approximately the same as that noted in pulmonary tuberculosis, the maximum and minimum figures being 120 and 79 respectively. The extremes however occurred, as in tuberculous meningitis, in the months of April and November.

Two facts of some importance emerge from the description of the curves in Figure 31. Firstly, the highest point in the seasonal trend of mortality from pulmonary tuberculosis occurred one month earlier, and the lowest point two months earlier than the corresponding dates for the other forms of the disease. It is probable that the reason for this difference lies in the fact the pulmonary tuberculosis is more readily activated by intercurrent disease than non-pulmonary tuberculosis, so that the maximum fatality from the former tends to occur somewhat earlier in the year than the maximum fatality from the latter. Extreme examples of this difference may be noted in epidemic years, and it should be recalled that the influenza epidemic of 1929, and to a less extent that of 1922, accelerated the usual seasonal trend of pulmonary tuberculosis so that the maximum mortality in these years was observed in January and in February/

February respectively. But no such change was noted in the mortality from the other forms of the disease, for in both years the highest death rate was recorded in April. In tuberculosis, therefore, the seasonal variation in mortality partly depends on the extent to which different forms of the disease may be adversely affected by other illnesses.

The second point to note from the curves in Figure 31 is that the seasonal excursion indicating the mortality from meningeal tuberculosis is much greater than that occurring from other forms of the disease. It must not be inferred from this result that tuberculous meningitis, as such, presents a greater seasonal variation than is encountered in other forms of tuberculosis. It is necessary to recall the fact that the average age of the patient dying from meningitis is much less than the average age of patients dying from pulmonary or other forms of tuberculosis. Possibly the explanation of the findings recorded is that children are more susceptible to seasonal influences than older people. This possibility will be investigated in a later section.

C. Seasonal Variation in the Mortality from Tuberculosis in Male and Female Sexes.- The Annual Reports of the Registrar General for Scotland do not contain details of the monthly number of deaths from different causes in each sex. These data, however, /

however, became available for the Sixteen Principal Towns in the year 1922, being published in the Monthly Returns. Since the year 1922 was an epidemic year, the present investigation was not commenced until 1923. For similar reasons the years 1929 and 1933 were not incorporated in this inquiry, so that the observation extended from 1923 to 1932 (excluding 1929).

It was especially necessary to avoid years in which epidemics occurred not only because the normal seasonal trend in tuberculosis mortality was disturbed, but also because the sexes themselves were not equally affected. The influenza epidemic of 1929, for instance, was much more severe on the female sex than on the male.

Figure 32 (page 132) represents in graphic form the extent to which the fatality from tuberculosis (all forms) amongst the male and female sexes of the Sixteen Principal Towns of Scotland was influenced by the seasons. The data from which this graph was constructed are to be found in Appendix IV, Table 4, (page 255). It will be noted from this figure that the seasonal variation in mortality was slightly more pronounced in the male sex than in the female sex. The difference, however, was not very great, and when investigated statistically it was found that there was a probability of 1 in 6 that it was due to chance and therefore the result could not be regarded as significant. ($\chi^2 = 15.6 : p = \text{approximately } 0.16.$)

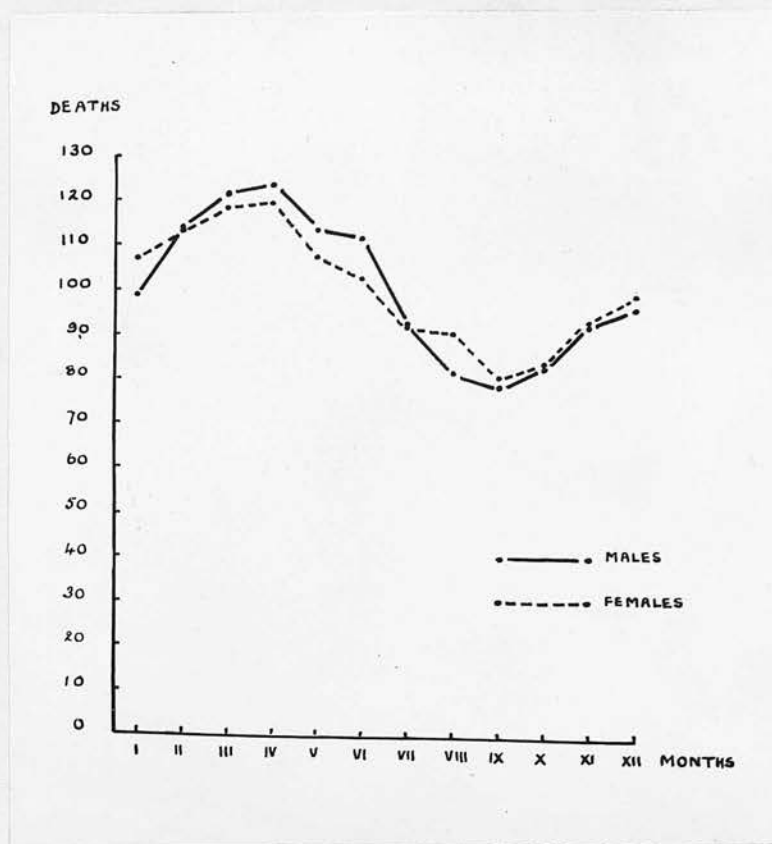


Figure 32.- Scotland, Principal Towns, 1923-1932 (excluding 1929). Monthly distribution of 1,200 deaths from tuberculosis (all forms) in male and female sexes.

The above results may be compared with those of the only similar inquiry known to the writer, namely that of Gottstein (1930). The latter author investigated the difference in seasonal variation in mortality between the sexes in Switzerland during the period from 1892 to 1900, but his observation was made in relation to pulmonary tuberculosis. Scientific comparison between the two investigations is therefore not possible, but it is interesting to note that/

that Gottstein also obtained results which apparently indicated that the male sex was more affected by seasonal influences than the female sex. The actual figures for both investigations may be consulted in Table 16.

Table 16.- Seasonal variation in the mortality from tuberculosis in male and female sexes. In this table the figures represent the monthly distribution of 1,200 deaths. (The data for Switzerland are taken from an investigation by Gottstein, 1930.)

Month	Scotland 1921-1930		Switzerland 1892-1900	
	Tuberculosis (all forms)		Tuberculosis (pulmonary)	
	Males	Females	Males	Females
I	99	107	104	103
II	114	113	120	110
III	121	118	133	124
IV	123	119	134	128
V	113	107	123	123
VI	111	102	109	108
VII	92	91	91	97
VIII	81	90	70	86
IX	78	80	74	78
X	82	83	72	76
XI	91	92	77	81
XII	95	98	87	87
Total	1200	1200	1194	1201

Although the difference between the sexes in Switzerland was apparently greater than that noted in Scotland, the absolute seasonal variation was also/

also more pronounced, and therefore it is unreliable to draw any inferences in the absence of statistical confirmation of the results. But statistical investigation was not carried out, nor is it possible to make the necessary calculations from the published figures in order to arrive at a decision on the point. (Apart from the fact that the totals do not add up to 1,200-which is not commented on by the author - the actual number of deaths for each month is not given.)

It can only be concluded, therefore, that no difference between the sexes in respect of seasonal variation in the mortality from tuberculosis has been proved to occur.

The fact referred to above, that the seasonal fluctuation in the mortality from pulmonary tuberculosis in Switzerland was more pronounced than the corresponding change in all forms of tuberculosis in Scotland, will call for attention later in this work.

II SEASONAL VARIATION IN THE GENERAL MORTALITY AND IN SELECTED CAUSES OF DEATH

A. Seasonal Variation in the General Mortality.-

It is now necessary to estimate the seasonal variation in the mortality from all causes of death, and to compare the result with that already noted in tuberculosis. The curves in Figure 33 (page 135) provide/

provide a graphic indication of the results for the decade 1921 to 1930, based on the distribution of 1,200 deaths. The figures from ^{which} the graph was constructed are to be found in Appendix IV, Table 5, (page 256).

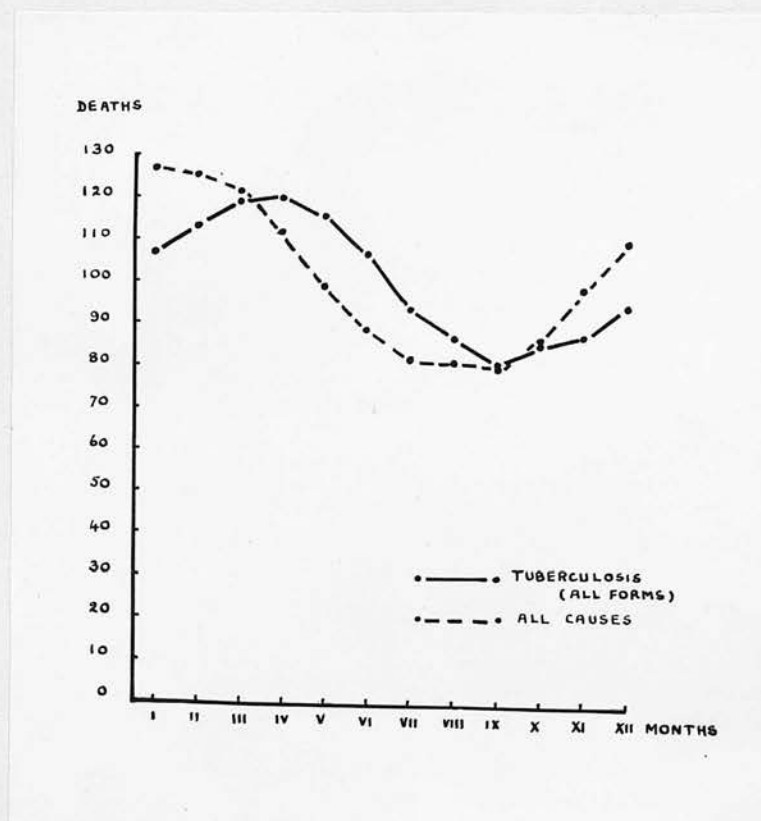


Figure 33.- Scotland, 1921-1930. Monthly distribution of 1,200 deaths from tuberculosis (all forms), and from all causes of death.

It will be noted at once that the maximum mortality from all causes occurred in the month of January, and from tuberculosis in April.

This statement, however, requires further attention. During the decade 1921 to 1930 epidemics of influenza occurred in January 1922 and January 1929, /

January 1929, and were accompanied by an unusual increase in the mortality from the acute respiratory infections. It cannot therefore be assumed that the curve in Figure 33 depicting the seasonal incidence of 1,200 deaths from all causes, represents a normal distribution.

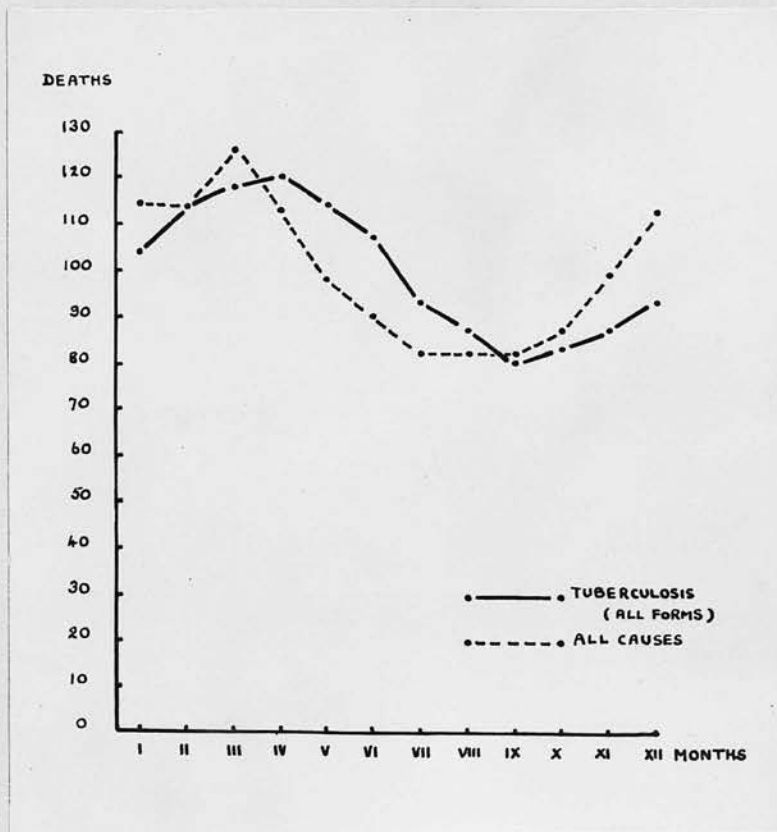


Figure 34.- Scotland, 1921-1932, (excluding 1922 and 1929). Monthly distribution of 1,200 deaths from tuberculosis (all forms), and from all causes of death.

Accordingly the years 1922 and 1929 were excluded from the period under review, and the years 1931 and 1932 were incorporated. The necessary re-calculations were made in order to present the distribution of 1,200 deaths from all causes and from tuberculosis/

tuberculosis during a more normal period. The results of this procedure may be seen on reference to Figure 37 (page 136) and to Appendix IV, Table 6, (page 256).

It should now be noted that the maximum mortality from all causes occurred in the month of March whilst that from tuberculosis, being little altered, was again observable in the month of April. Throughout the year the seasonal trend in the mortality from tuberculosis lagged from one to two months behind that noted in all causes of death. The excursion of the curve above and below the mean of 100 deaths per month was slightly greater in the general mortality than in tuberculosis.

B. Seasonal Trends in Mortality from Selected Causes of Death.- It is unnecessary to consider the seasonal trends in mortality from a wide variety of conditions. The behaviour of the infectious diseases is too well known to necessitate anything more than passing reference. Measles and Whooping-cough attain their greatest fatality rate during February and March. Scarlet fever causes more deaths in the autumn than in the spring. Diphtheria is not quite so regular in its seasonal occurrence, and sometimes seems to favour the spring and sometimes the autumn.

In the present investigation attention will be devoted to the following diseases: Influenza, /

have been even more pronounced.

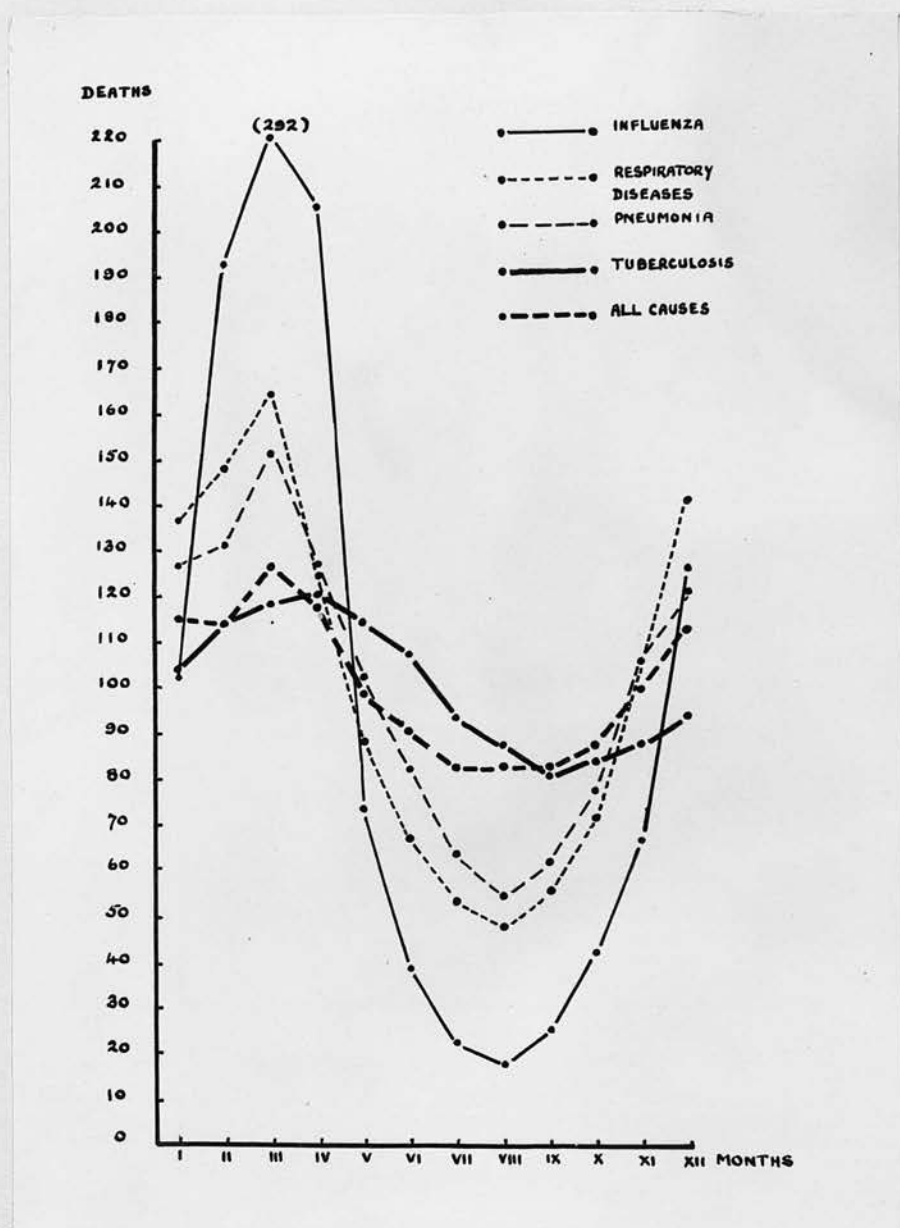


Figure 35.- Scotland, 1921-1932 (excluding 1922 and 1929). Monthly distribution of 1,200 deaths from various causes.

Respiratory Diseases.- The five main causes of death among diseases of the respiratory system (excluding tuberculosis) are as follows: Bronchitis,/

Bronchitis, Broncho-pneumonia, Pneumonia, Pleurisy and Congestion of the Lung. All other respiratory affections are relatively infrequent causes of death. The seasonal mortality from this group of diseases was much less pronounced than that observed in influenza, but still exhibited a seasonal reaction very much greater than that observed in tuberculosis and in all causes of death, with which it can be compared in the same figure.

Pneumonia.— Apart from respiratory disease in general, reference is made to pneumonia on account of the fact that the virulence of the pneumococcus has been stated to vary at different times of year (Gaskell, 1927). In the Reports of the Registrar General pneumonia includes all cases of lobar pneumonia, and all other forms not registered as tuberculous or broncho-pneumonia. The seasonal trend observed in the monthly distribution of 1,200 deaths from this disease, was somewhat less striking than that noted above in the main group of respiratory diseases, but was still much more pronounced than the variation described in tuberculosis and in all causes of death. It will be seen, however, that the highest and lowest points in the curve occurred one month earlier than the corresponding reading for tuberculosis.

Cancer.— The seasonal distribution of 1,200 deaths from malignant disease is recorded in Figure 36. Slight alterations in the monthly proportion of/

of deaths was observed to occur but no seasonal trend could be inferred.

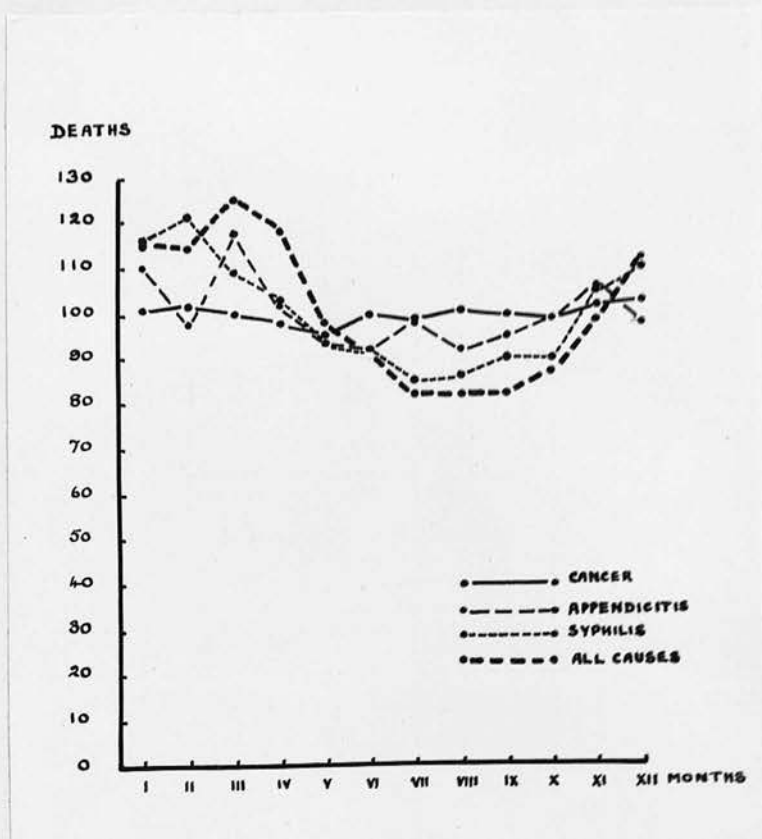


Figure 36.- Scotland, 1921-1932 (excluding 1922 and 1929). Monthly distribution of 1,200 deaths from various causes.

Appendicitis.- In Scotland between 400 and 500 people die from appendicitis each year. The monthly variations in mortality are represented in Figure 36. The curve was somewhat irregular due to the relatively small number of deaths. This irregularity was observed chiefly in the month of February but nevertheless a seasonal trend could be defined. The maximum/

maximum number of deaths occurred in March. There ensued a steady diminution during April, May and June. The mortality remained low during the summer but commenced to increase during the autumn. It will be noted from Figure 36 that the seasonal trend was very much less pronounced than that from all causes of death.

Syphilis.- Syphilis is not recorded as a common cause of death, but in conjunction with General Paralysis of the Insane and with Tabes Dorsalis it was found that about 400 or 500 deaths are registered each year. A definite seasonal trend in mortality was noted, which although more pronounced than that occurring in appendicitis was less marked than the trend observed in all causes of death. In connection with seasonal variation in syphilis it is interesting to recall that positive serological reactions are stated to be most common in February, March and April than at other times of year (Spillman, 1927). The maximum mortality in the present investigation was noted in February but rapidly diminished during March and April.

III THE RELATIONSHIP OF AGE TO SEASONAL VARIATION IN MORTALITY

Reference has already been made to the fact that an examination of the seasonal trend in the mortality//

mortality from tuberculous meningitis revealed a much more marked fluctuation than was observed in pulmonary tuberculosis. It was suggested that this might indicate greater susceptibility on the part of young subjects to seasonal influences than that encountered amongst older people. It is now proposed to examine this possibility a little more closely, both in relation to tuberculosis and to the general mortality.

The period under statistical review was extended to incorporate thirteen years between 1912 and 1932. This was done in order to base the ensuing observations on as large a number of fatal cases as possible, because the necessary information was not available for the whole of Scotland. The data quoted hereafter refer only to the Sixteen Principal Towns, and were derived from an analysis of the Monthly Returns of the Registrar General. The years 1915 to 1919 were excluded from the period under consideration on account of the Great War, whilst the years 1922 and 1929 were also rejected on account of influenza epidemics.

The number of fatal cases of tuberculosis occurring during the thirteen years for which data were collected, was insufficient to allow reliable calculations to be made for each of the twelve age groups customarily employed by the Registrar General. Accordingly in this inquiry the monthly distribution of 1,200 deaths was computed for five larger age groups as follows: /

as follows:

- (1) Below 5 years
- (2) From 5 years to 15 years
- (3) From 15 years to 25 years
- (4) From 25 years to 45 years
- (5) Above 45 years

The results of this inquiry will be presented firstly, in respect of tuberculosis, and secondly, for all causes of death.

A. The Relationship of Age to the Seasonal Variation in the Mortality from Tuberculosis.- The differences encountered in the seasonal trend in the mortality from tuberculosis in the five age groups defined above are illustrated in Figure 37.

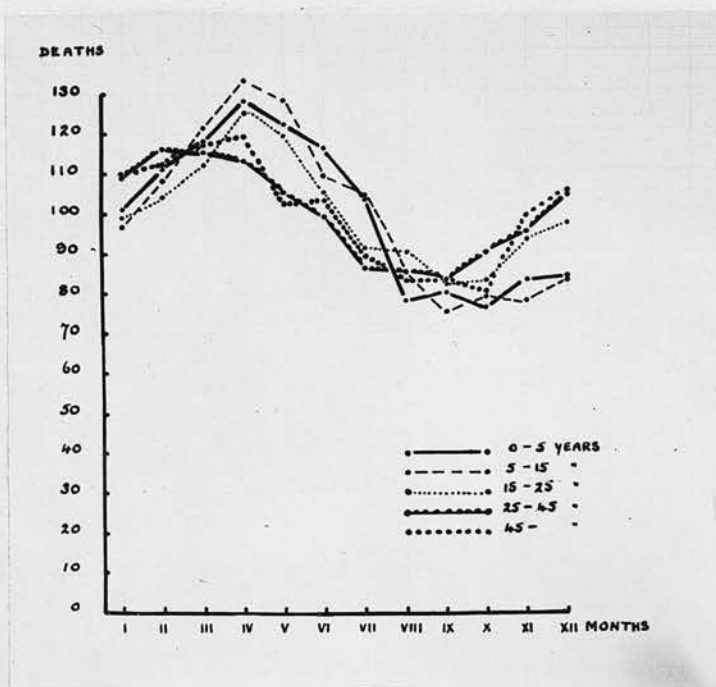


Figure 37.- Scotland, Sixteen Principal Towns, 1912-1932 (excluding 1915-1919, 1922 and 1929). Monthly distribution of 1,200 deaths from tuberculosis (all forms) in different age groups.

It can be noted from Figure 37 that in tuberculosis the human subject is apparently most susceptible to seasonal change between the ages of 5 and 15 years. The next age group most readily affected is that below 5 years, and then the period between 15 and 25 years. In the age groups above 25 years the tuberculous subject is apparently somewhat less influenced by seasonal change.

The data on which these curves were based are to be found in Appendix IV, Table 9, (page 259). The table also incorporates the values of "Chi-squared", for it was necessary to ascertain if the differences in the results were of real significance. It was found that the difference between the age groups 0-5 years and 5-15 years was not significant. There was, however, a genuine difference in the seasonal variation observed between the age groups 5-15 years and 15-25 years, and again a real difference between the age groups 15-25 years and 25-45 years. There was no significant difference in the seasonal variation in mortality from tuberculosis relating to the two age groups above 25 years of age.

On the whole therefore, it may be concluded that the tuberculous subject is most susceptible to seasonal variation below the age of 15; somewhat less susceptible to such change between the ages of 15 and 25 years; whilst above the age of 25 there is evidence of diminishing seasonal change.

B. The Relationship of Age to Seasonal Variation in the General Mortality.- The monthly distribution of 1,200 deaths from all causes in each of the selected age groups during the period of observation is recorded graphically by means of the five curves in Figure 38. The data from which this figure was constructed may be referred to in Appendix IV, Table 10, page 260.

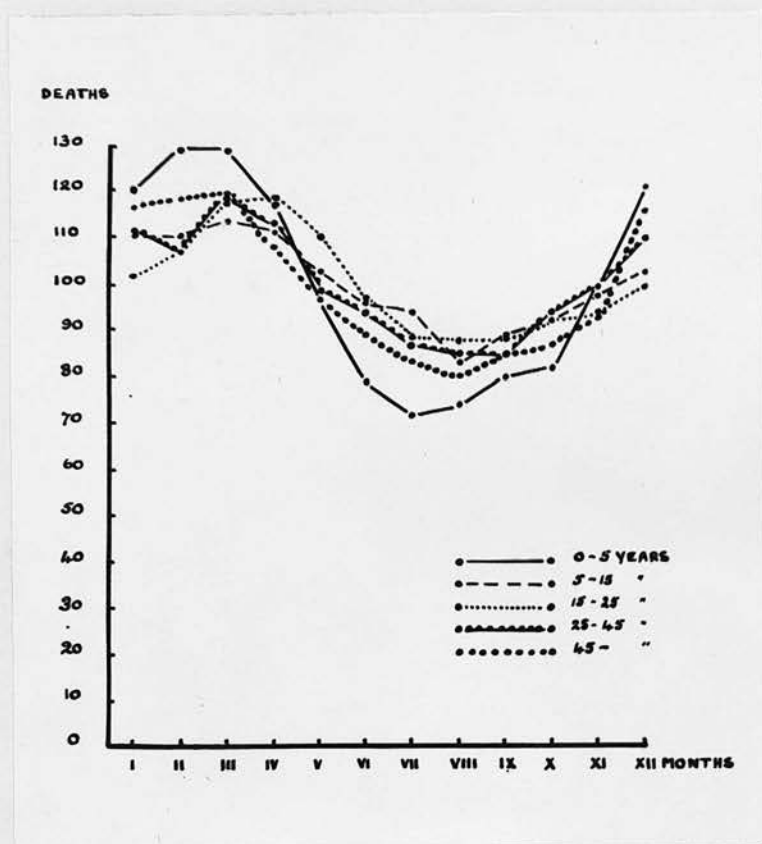


Figure 38.- Scotland, Sixteen Principal Towns, 1912-1932 (excluding 1915-1919, 1922 and 1929). Monthly distribution of 1,200 deaths from all causes in different age groups.

From the above figure it will be noted that the age group 0-5 years was much the most susceptible to/

to seasonal variation in mortality, whilst the age group 5-15 years was least affected. The age groups 15-25 years and 25-45 years both exhibited a decided increase in the seasonal fluctuation in mortality as compared with the corresponding change noted in the age group 5-15 years, whilst the period above 45 years of age presented a still further increase as compared with the age group 25-45 years.

Since all these curves were based on large numbers, there was in most instances little doubt that the recorded differences between the age groups were statistically significant. Nevertheless the "Chi-squared test" was performed in cases where doubt might possibly exist regarding the nature of the difference between two sets of curves. Where this was done the value of "Chi-squared" was incorporated in Appendix IV, Table 10. It was found that even the smallest difference between the curves in Figure 38, was statistically significant. It may be stated that the age group 0-5 years is the most susceptible to seasonal variation in mortality; the age group 5-15 years is least affected; whilst thereafter a gradual increase in the seasonal trend was observable, which however, never approaches in intensity the reaction noted in the first five years of life.

From the data presented above two important facts emerge. Firstly, it is clear that the seasonal/

seasonal trend in mortality varies at different ages. Secondly, it is apparent that in certain age groups the seasonal variation in the mortality from tuberculosis is widely different from that observable from all causes of death. The necessarily complicated nature of Figures 37 and 38, however, renders detailed comparison a matter of some difficulty, and in order to mark clearly the differences between them reference may be made to the curves in Figures 39 to 43.

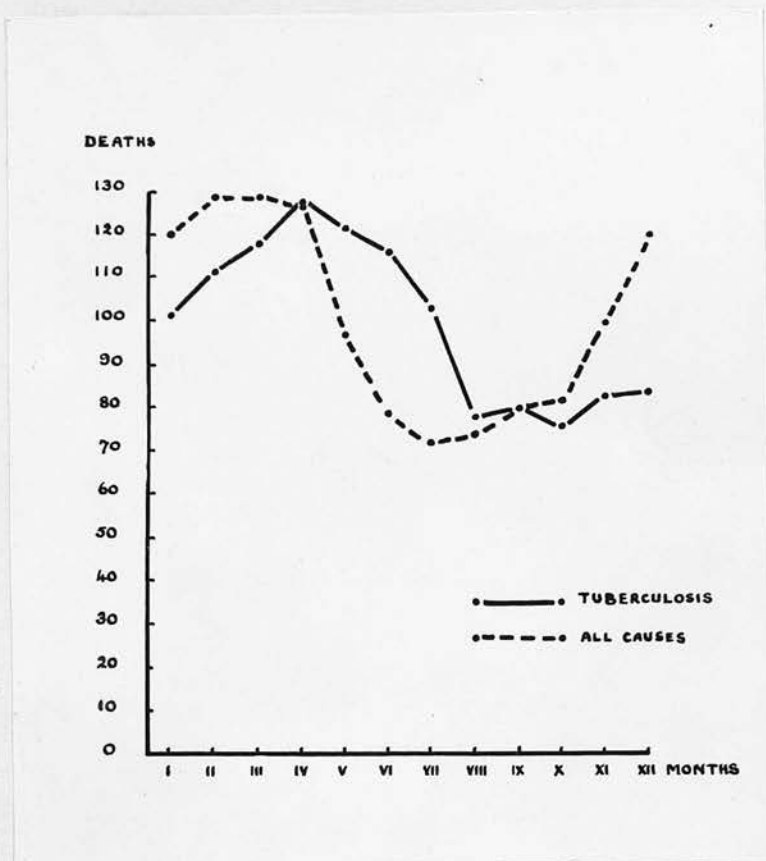


Figure 39.- Scotland, Sixteen Principal Towns, 1912-1932 (excluding 1915-1919, 1922 and 1929). Monthly distribution of 1,200 deaths in the age group 0-5 years from tuberculosis and from all causes of death.

In the age group 0-5 years for example (Figure 39, page 148), the difference between the curves representing the fatality from tuberculosis and from all causes was one of time rather than of degree. The excursion of the curves above and below the mean of 100 deaths per month was approximately similar, indicating little difference in the intensity of seasonal change. But it will be noted that the lag in the effect of the seasons on tuberculosis mortality as compared with the effect observed on the collected causes of death was very marked, there being for the most part two months of difference between corresponding points in the two curves.

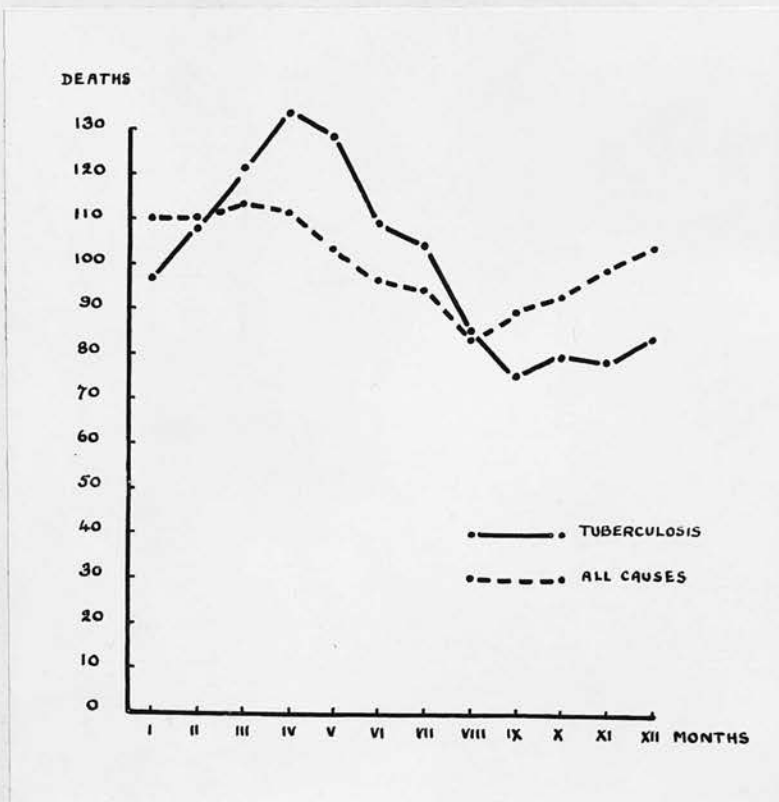


Figure 40.- Scotland, Sixteen Principal Towns, 1912-1932 (excluding 1915-1919, 1922 and 1929). Monthly distribution of 1,200 deaths in the age group 5-15 years from tuberculosis and from all causes of death.

In the age group 5-15 years (Figure 40, page 149) a very marked difference occurred. In tuberculosis the extent of the seasonal fluctuation was as great as at any age but in the general mortality the reverse was the case, the seasonal change being at its lowest intensity.

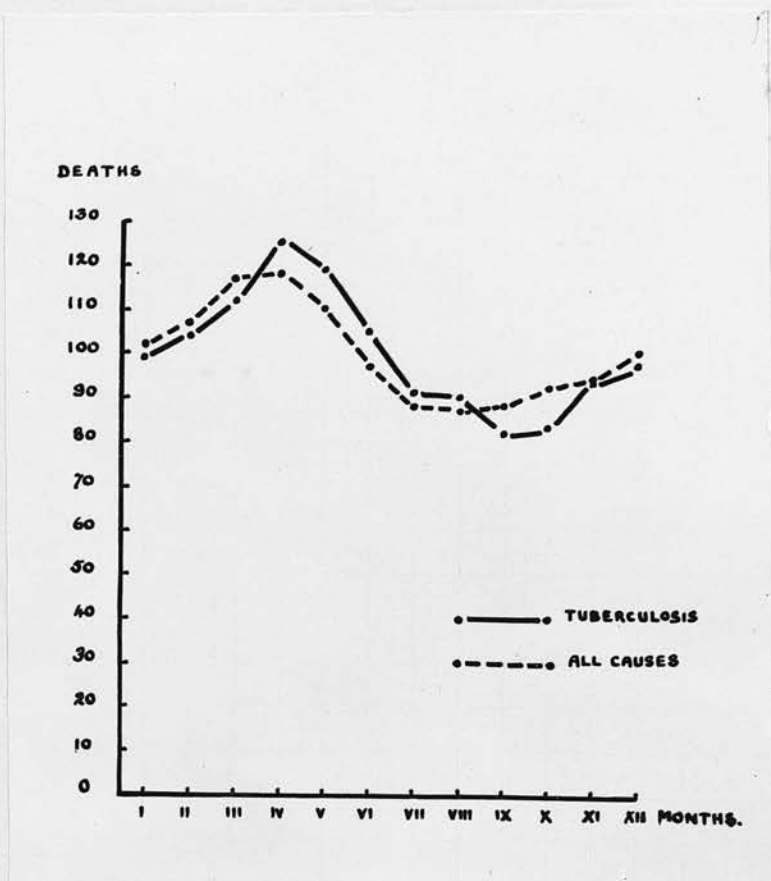


Figure 41.- Scotland, Sixteen Principal Towns, 1912-1932 (excluding 1915-1919, 1922 and 1929). Monthly distribution of 1,200 deaths in the age group 15-25 years from tuberculosis and from all causes of death.

In subsequent age groups the seasonal variation in the mortality from tuberculosis became less pronounced, whilst that from the general mortality/

mortality became more pronounced so that the two series of curves tended to fall more into line. But in the age group 15-25 years (Figure 41, page 150) a decided difference may still be observed, tuberculosis again exhibiting the greater seasonal trend.

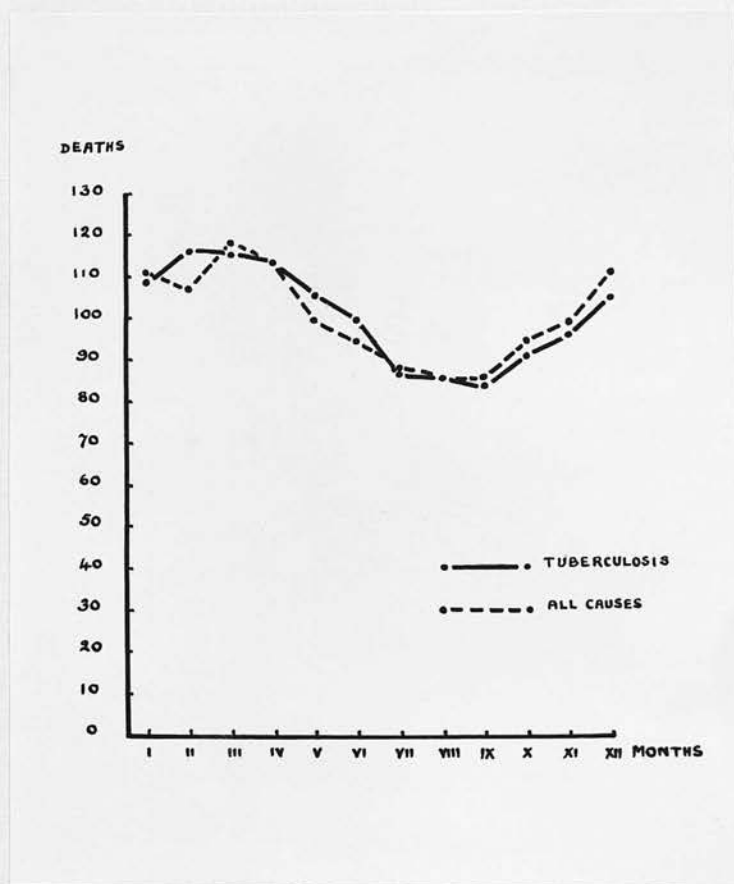


Figure 42.- Scotland, Sixteen Principal Towns, 1912-1932 (excluding 1915-1919, 1922 and 1929). Monthly distribution of 1,200 deaths in the age group 25-45 years from tuberculosis and from all causes of death.

In the age group 25-45 years (Figure 42) there was no appreciable difference in the extent of the seasonal change in the tuberculosis mortality as compared with the seasonal change in the general/

general mortality.

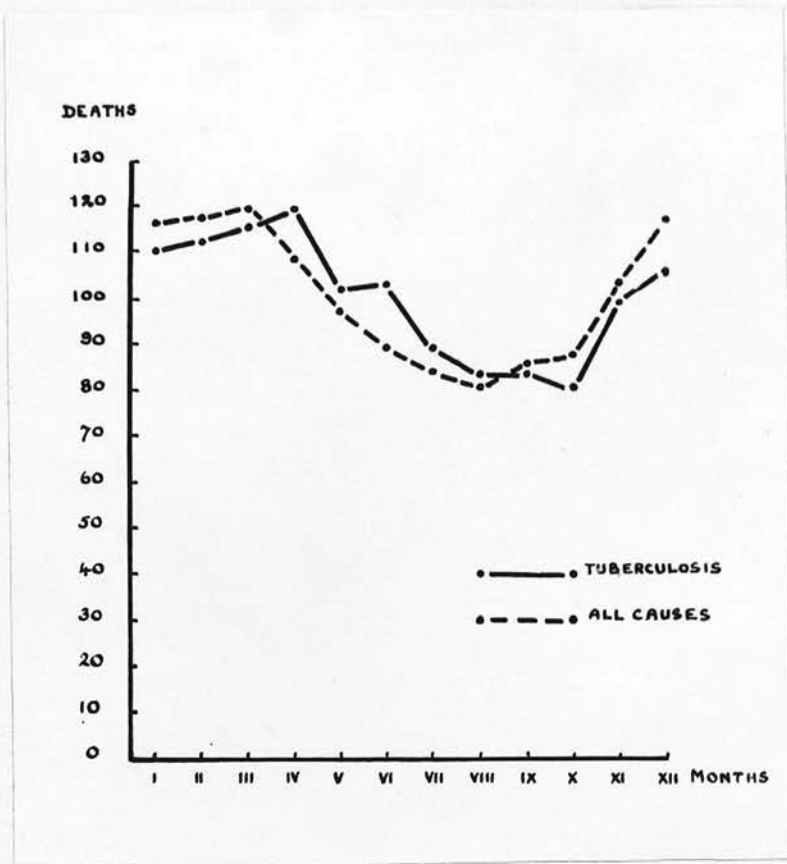


Figure 43.- Scotland, Sixteen Principal Towns, 1912-1932 (excluding 1915-1919, 1922 and 1929). Monthly distribution of 1,200 deaths in the age group above 45 years from tuberculosis and from all causes of death.

Above the age of 45 years (Figure 43) there was again very little difference in the degree of seasonal change as observed in tuberculosis and in the general mortality. But in this, as in other age groups, the seasonal trend in tuberculosis mortality lagged approximately one month behind the seasonal trend observed in all causes of death.

Summary.- The seasonal variation in the/

the mortality from tuberculosis is most pronounced below the age of 15 years; it is less marked between the ages of 15 and 25 years; and least marked above the age of 25 years.

In the general mortality seasonal variation is most marked below the age of 5 years; it is least marked between 5 and 15 years of age, and above 15 years of age it tends to increase again.

The chief differences, therefore, between tuberculosis and all causes of death in this respect are in the age group between 5 and 15 years of age. The difference is less pronounced, but still present in the age group 15 to 25 years.

IV THE RELATIONSHIP OF CLIMATE AND METEOROLOGY TO SEASONAL VARIATION IN THE MORTALITY FROM TUBERCULOSIS

The discussion of seasonal trends in disease entails some reference to climate and weather, since these two factors would appear to be largely responsible for the changes under consideration. Evidence will now be presented concerning the effects of climate and weather on seasonal variation in the mortality from tuberculosis.

A. The Relationship of Climate to Seasonal Variation in the Mortality from Tuberculosis.- The most satisfactory method of approaching this question is to compare the statistics of countries experiencing/

experiencing different climatic conditions. For this purpose it is proposed to consider certain data for Germany and to compare them with the results obtained by the writer in Scotland.

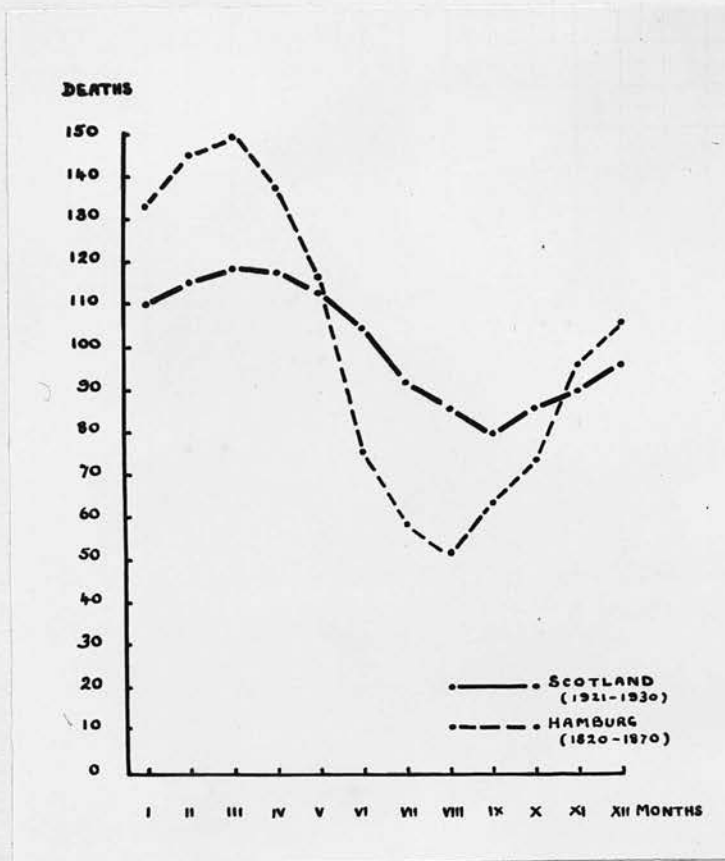


Figure 44.- Scotland, 1921-1930, and Hamburg, 1820-1870. Monthly distribution of 1,200 deaths from pulmonary tuberculosis.

This comparison is facilitated by reference to Figure 44 which is based upon the seasonal variation in the mortality from pulmonary tuberculosis as observed in Scotland from 1921 to 1930, and which has already been described (page 127), and upon the corresponding change in the city of Hamburg during the/

the period of 50 years from 1820 to 1870. The figures from which the curves are constructed may be consulted in Appendix IV, Table 11, (page 261).

It will be noted that the seasonal trend in the mortality from pulmonary tuberculosis was very much more pronounced in Hamburg than in Scotland. In Hamburg the highest and lowest points in the curve indicated a seasonal variation of approximately 50 per cent. above and below the mean of 100 deaths per month, whilst in Scotland the corresponding change amounted to only 20 per cent. above and below the mean. This would seem to indicate that the extremes of a continental climate like that of Germany, might possibly lead to more marked seasonal changes in mortality than those experienced in a more equable climate such as that of Scotland.

This deduction, however, cannot be advanced without further discussion since a period of 80 years elapsed between the mid points of the two observations compared above. It is theoretically possible that the influence of the seasons might have become less pronounced during the interval. This possibility was investigated in the preparation of Figure 45 (page 156). In this figure the seasonal trend of the mortality from pulmonary tuberculosis in the Principal Towns of Scotland may be compared in three quinquennia, namely, 1866 to 1870, 1890 to 1894, and 1926 to 1930. (Corresponding data for the whole of Scotland are not/

not available.) The figures on which these curves were based are to be found in Appendix IV, Table 12, (page 261).

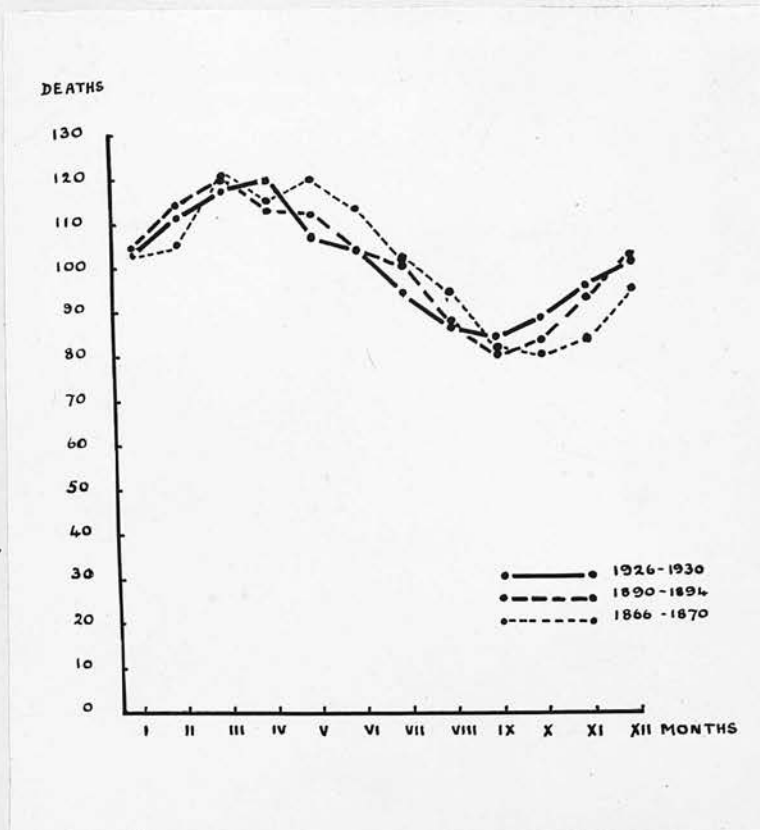


Figure 45.- Scotland, Principal Towns. Monthly distribution of 1,200 deaths from pulmonary tuberculosis during the quinquennia 1866-1870, 1890-1894, and 1926-1930.

From the above figure it will be observed that minor changes in the seasonal variation in the mortality from pulmonary tuberculosis occurred during the period under observation, but no diminution in the seasonal change has occurred in the last 70 years. Since this is so in Scotland it is probably safe to assume that in Hamburg the seasonal trend has not

not diminished either, and that the curves in Figure 44 are strictly comparable, despite the interval in time between the periods they represent.

In this connection reference may be made again to the figures compiled by Gottstein for Switzerland during the period 1892 to 1900 (page 133). Mention was made above that the actual seasonal variation in the mortality from pulmonary tuberculosis in Switzerland was greater than that in Scotland for all forms of tuberculosis. On making the stricter comparison between the seasonal variation in pulmonary tuberculosis in both localities, it was found that in Switzerland the seasonal fluctuation exhibited a variation of 30 per cent. above and below the mean of 100 deaths per month as against 20 per cent. in Scotland.

The available evidence, therefore, would seem to indicate that the continental type of climate is associated with more pronounced seasonal variation in the mortality from pulmonary tuberculosis than the insular type of climate.

B. The Relationship of Meteorology to Seasonal Variation in the Mortality from Tuberculosis.- Modern opinion tends to attribute less importance to meteorological change in relation to tuberculosis than formerly. But nevertheless the investigation of the influence of weather on seasonal change in tuberculosis is essential for the discussion of the present work.

Chabaud (1928) attempted to correlate the complications of therapeutic pneumothorax with meteorological conditions. He observed the effusion of fluid in 259 cases, and the bilateralisation of lesions in 184 cases, but could not determine any relationship to weather conditions. Paquet (1931), on the other hand, stated that the fatality rate in France was associated with rainfall, and was higher in rainy years than in dry years.

The relationship of acute respiratory infections to meteorological conditions is undoubted. Woods and Stallybrass (1932) found that a high degree of correlation existed between the respiratory mortality among young adults in Liverpool, and the mean temperature (and the temperature of evaporation) for the week during which death took place, and for a period of two weeks before death. In the acute respiratory infections however, in which a fatal issue, or alternatively the commencement of convalescence, is established within a few days, such an investigation may be readily undertaken. But in tuberculosis, perhaps the most chronic of diseases, this direct relationship between weather and fatality if it exists cannot be determined since the results of meteorological abnormalities are seldom immediately apparent. The time interval between cause and effect is so extended that correlation becomes untrustworthy.

But although the method of Woods and Stallybrass/

Stallybrass cannot be readily utilised in order to ascertain the relationship of meteorological conditions in the mortality from tuberculosis, by reason of its great chronicity, it was hoped that the investigation of the following three problems would afford, in a less direct way, similar information.

(1) Is the seasonal fluctuation in the mortality from tuberculosis reasonably constant, or do definite variations occur from year to year?

(2) If the changes postulated under paragraph (1) above are actually noted, do other diseases known to be influenced by meteorological conditions present similar phenomena?

(3) In the event of the variations suggested under paragraphs (1) and (2) above being successfully demonstrated, do the meteorological records for the appropriate years furnish any abnormal features which might be associated with unusual seasonal trend in mortality?

Inquiries along these three lines were instituted, and the results are presented below.

(1) Variations in the Seasonal Trends in the Mortality from Tuberculosis.- Reference to Figure 29 (page 124), will reveal the fact that the seasonal fluctuation in the death rate from tuberculosis during the years 1927 and 1928 was apparently less pronounced than during the rest of the decade 1921 to 1930. Since, however, the death rate was declining from year to/

to year it was necessary to ascertain the monthly distribution of 1,200 deaths for each of these two periods. The result of this procedure is recorded in Figure 46. The data on which this figure is based

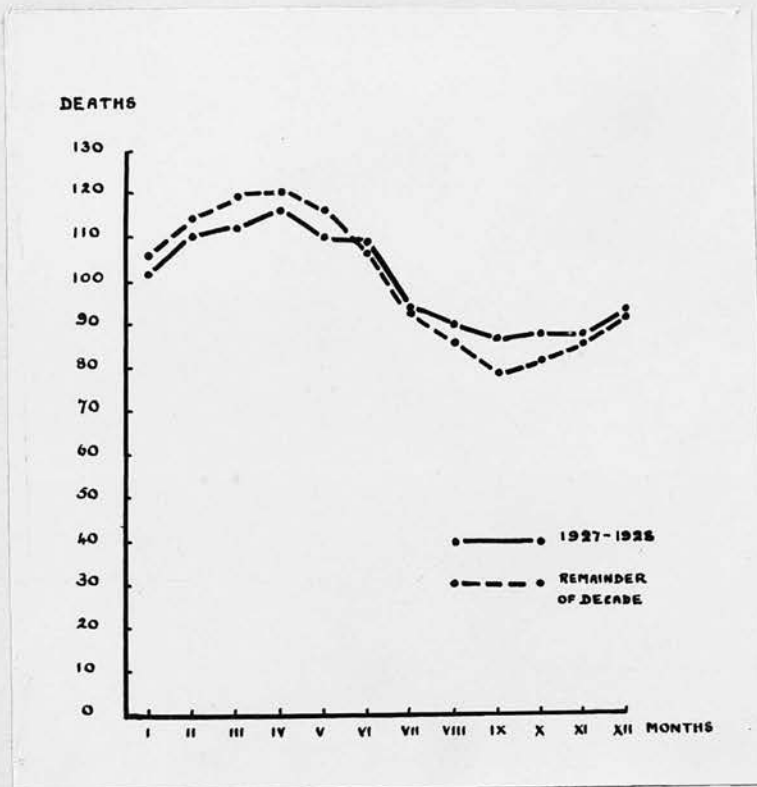


Figure 46.- The monthly distribution of 1,200 deaths from tuberculosis (all forms) during 1927-1928, and during the remainder of the decade 1921-1930.

are to be found in Appendix IV, Table 13, (page 262). The figures for epidemic years were not incorporated. It will be observed from the above figure that the seasonal curve was definitely flattened during the years 1927 to 1928, as compared with the remainder of the decade. The probability of this result being/

being due to chance was only 1 in 16, and therefore the difference between the two curves might be considered genuine.

(2) Seasonal Variation in the Mortality from Certain Diseases known to be Influenced by Meteorological Conditions: (a) Diarrhoea and Enteritis (under two years).- One of the diseases bearing the most striking relationship to meteorological conditions is the so called "Summer Diarrhoea" of infants. Figure 47 represents the monthly distribution of 1,200 deaths from this disease in Scotland during 1927 and 1928, and during the remainder of the decade 1921 to 1930.

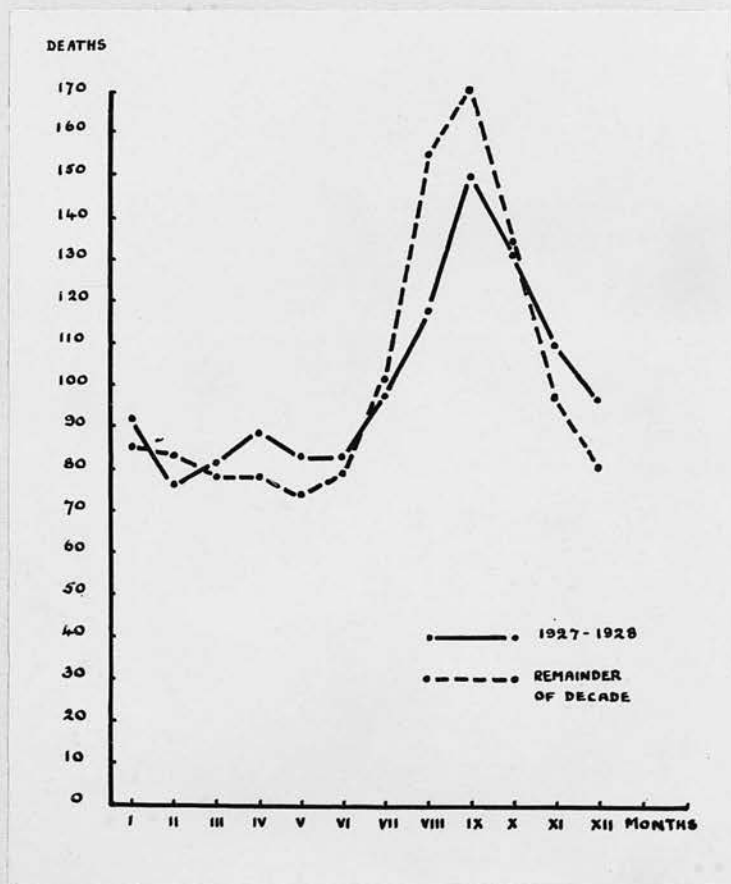


Figure 47.- The monthly distribution of 1,200 deaths from diarrhoea and enteritis (under two years) in Scotland during 1927-1928, and during the remainder of the decade 1921-1930.

The figures upon which the above graph was based are to be found in Appendix IV, Table 14, (page 262). It will be noted that although the type of change is entirely different from that observed in relation to tuberculosis, since it attained its maximum in August and September, and its minimum in March, April and May, the relative flattening of the seasonal trend in mortality during the years 1927 and 1928 was again in evidence. Statistical investigation showed that the probability of this result being due to chance was only about 1 in 40. The difference between the two periods under observation was therefore considered to be significant.

(b) Bronchitis and Pneumonia.— The graph in Figure 48 (page 163) represents the distribution of 1,200 deaths from bronchitis and pneumonia in Scotland during the years 1927 and 1928, and during the remainder of the decade 1921 to 1930. The data on which this figure was based are to be found in Appendix IV, Table 15, (page 263). Once again it will be noted that the maximum and minimum points in the curves depicting the seasonal fluctuation of mortality during the years 1927 and 1928 were nearer to the mean than during the remainder of the decade, indicating a less pronounced seasonal change at that time.

Figure 48/

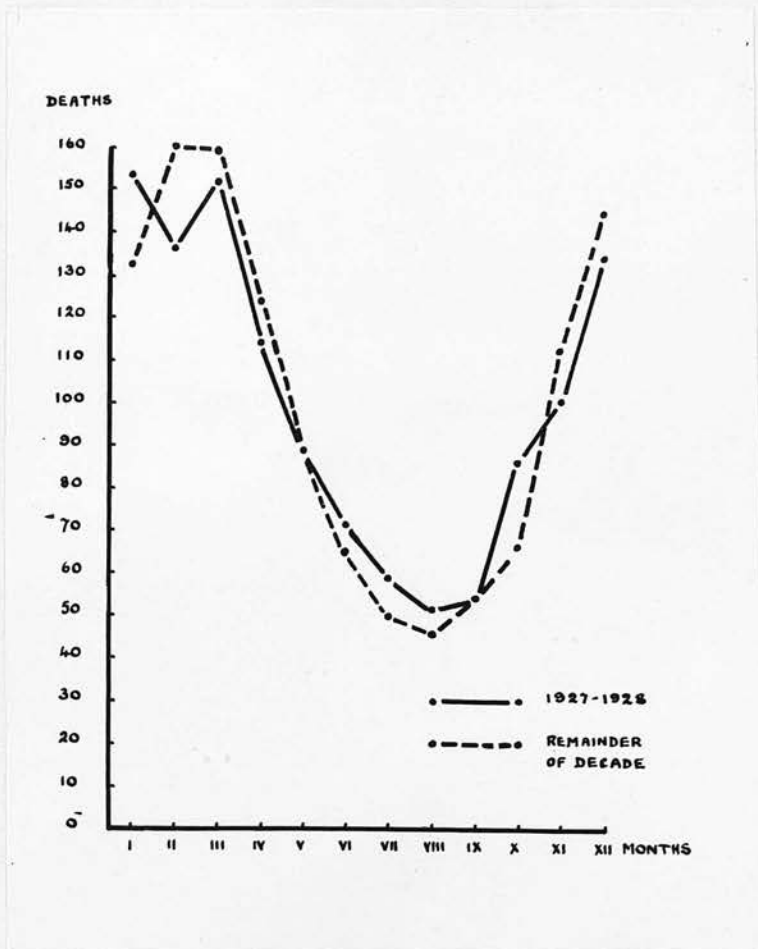


Figure 48.- The monthly distribution of 1,200 deaths from bronchitis and pneumonia in Scotland during 1927-1928, and during the remainder of the decade 1921-1930.

The difference between the two curves in the above figure is apparently slight. But the result was based on very large numbers since bronchitis and pneumonia were both common causes of death, and the result was found to be statistically significant.

It would therefore appear that in tuberculosis, and in certain diseases known to be affected by meteorological factors, namely diarrhoea and enteritis/

enteritis in infants, and bronchitis and pneumonia, the seasonal fluctuation in the incidence of death was less marked during the years 1927 and 1928 than during the remainder of the decade 1921 to 1930.

(3) Comparison of the Meteorological Conditions of the Years 1927 and 1928 with those Obtaining During the Remainder of the Decade 1921 to 1930.- If meteorological influences were of great importance in the production of seasonal variation in mortality, it would be reasonable to suppose, in view of the seasonal reactions encountered in the diseases described above, that some decided difference would be observable between the meteorological records of the two periods named.

The main meteorological elements which are likely to influence disease are sunshine, temperature, relative humidity and rainfall. No monthly sunshine returns are published for Scotland, but the writer was allowed to abstract the unpublished Sunshine Lustra compiled by the Meteorological Office of the Air Ministry, for which kindness he is indebted to Major Goldie, the Superintendent. The remaining data were obtained from the Monthly Returns of the Registrar General for Scotland.

In order to ascertain the average weather conditions experienced by the population of Scotland during the years 1921 to 1930 no data were incorporated from the very remote meteorological stations.

An undue proportion of records from sparsely inhabited districts would have given no reliable indication of the type of weather experienced by the population as a whole. Observations were therefore selected from eleven meteorological stations representative of an area in which the vast majority of the population was resident.

Sunshine.- The necessary calculations were made to determine from the available data the average monthly amount of sunshine, in hours, for the eleven meteorological stations during the years 1927 and 1928, and for the remainder of the decade. The results are to be found in Appendix IV, Table 16, (page 264). They revealed the fact that there was a relative diminution in the amount of sunshine during the former period as compared with the latter. The deficiency was observable in varying degrees from March to July, and from October to December. The slight excess of sunshine during January, February and September was not sufficient to compensate for the lack of sunshine during the rest of the year, but, in fact, tended further to diminish the seasonal difference between summer and winter. On the whole it may be stated that the sunshine curve was flattened during the years 1927 and 1928, suggesting a possible relationship between variations in the amount of sunlight and the seasonal trend in the mortality from certain diseases/

diseases including tuberculosis.

This hypothesis, however, was rendered untenable by the fact that the years 1927 and 1928 did not constitute the only part of the decade during which a relative diminution in the amount of sunlight was observable. Reference to Appendix IV, Table 16, (page 264) will show that the deficiency of sunshine during the years 1923 and 1924 was as great or greater than that experienced during 1927 and 1928. But as will be noted from Figure 29 (page 124), the seasonal variation in the mortality from tuberculosis during these two years was as pronounced as that recorded during any other years of the decade.

It may be stated, therefore, that variations in the amount of sunshine during the decade 1921 to 1930, were not sufficiently marked to affect the seasonal trend in the mortality from tuberculosis.

Rainfall.- The average rainfall for the principal meteorological stations of Scotland during the decade 1921 to 1930 may be consulted in Appendix IV, Table 17, (page 264). It will be noted that the two years 1927 and 1928 were the wettest years of the decade, the percentage amount of the normal rainfall being 119. During the remaining years of the decade the percentage amount of rainfall was 106. The question arises, therefore, whether the diminished seasonal change in the mortality from tuberculosis during the former period was associated with the/

the increased precipitation.

On theoretical grounds it is not unreasonable to suppose that an unusually dry winter and spring followed by an unusually wet summer and autumn might tend to cause a relative diminution in the mortality from tuberculosis during March and April, and a relative increase in the mortality in September and October, which were characteristics of the seasonal trend actually observed in the years 1927 and 1928. In point of fact, however, the increased precipitation during these years was especially noted in January, and from August to November, or more generally in the first and third quarters of these years. Now if this excessive rainfall in the third quarter were responsible for an increase in the anticipated mortality from tuberculosis during the late summer and autumn, the abundant rainfall during the first quarter of the year would, it might be supposed, have led to an unusual increase in the mortality during the spring. In actual fact however the increase in the mortality which is expected at that time of year was much less than usual.

As far as can be ascertained, therefore, irregularities in rainfall are not closely associated with changes in the seasonal variation in the mortality from tuberculosis.

Mean Temperature.- The mean temperatures for the decade 1921 to 1930 are to be found in Appendix IV, Table 13, (page 265). On comparing the data for each/

each month during the years 1927 and 1928 with the average of the recordings for the remaining years of the decade, very little difference was encountered. Only the figures for the month of June differed to any extent, the averages being 51.7°F. for the years 1927 and 1928, and 55.4°F. for the remainder of the decade. This was a relatively marked difference, but since it was restricted to one month only it seems improbable that it can be correlated with the variations in the seasonal trend of mortality which have been described.

Relative Humidity.- Figures indicating the relative humidity in Scotland during the decade 1921 to 1930 have been recorded in Appendix IV, Table 19, (page 265). Examination of these data showed that the only differences between the two periods under review were during the months of April, May and November when slightly lower figures were registered for the years 1927 and 1928. It is extremely unlikely that such differences could cause a diminution in the seasonal trend in the mortality from tuberculosis and other diseases during that period.

Summary and Conclusion.- Since the effects of weather on seasonal variation in the mortality from tuberculosis cannot be investigated in the usual way owing to the chronicity of the disease, an endeavour has been made, in a less direct way, to trace a possible connection between a period of unusually restricted seasonal change in the mortality from tuberculosis/

tuberculosis (and from certain other diseases), and the meteorological conditions obtaining during that period. Attention was devoted to sunshine, rainfall, mean temperature and humidity.

From the evidence advanced no connection can be determined between weather and seasonal change in the mortality from tuberculosis. It is impossible, however, to state definitely that such a relationship does not exist since it is undoubtedly an important factor in the causation of the seasonal trend in the acute respiratory infections and in other diseases.

V SEASONAL VARIATION IN MORTALITY: SUMMARY

The study of the incidence of death in a population month by month reveals the fact that a certain seasonal trend occurs in the general mortality, and this, when not disturbed by unusual circumstances, may be termed the natural or expected seasonal variation in mortality. The maximum number of deaths is recorded in March and the minimum in July and August. This seasonal trend may be noted at all ages, but is greatest below five years of age, least during the school years (5 to 15 years), and gradually increases thereafter, but is never again so marked as it was below five years of age.

Certain diseases exhibit a very marked seasonal trend in mortality, and these include many of the/

the infective diseases especially influenza and the acute respiratory infections.

In certain other conditions, deaths occur with little seasonal incidence. In syphilis and appendicitis, for example, the seasonal trend is less marked than in all causes of death, whilst in malignant disease no seasonal tendency whatever can be noted.

In tuberculosis the seasonal trend in fatality is somewhat peculiar. The maximum mortality occurs in April, and the minimum in September, that is respectively one to two months later than the corresponding points for the general mortality. During April and May the proportion of deaths from tuberculosis diminishes slowly whilst the number of deaths from all causes declines rapidly. Conversely in November and December while the proportion of deaths from tuberculosis is increasing slowly, the number of deaths from all causes is increasing very rapidly. The seasonal trend in the mortality from tuberculosis lags behind the natural trend observable in the collected causes of death.

The above noted lag, however, is not so noticeable in pulmonary tuberculosis as in other forms of the disease. The greatest number of deaths from pulmonary tuberculosis occurs in March, which is equal in point of time to the maximum general mortality. But the minimum number of deaths from pulmonary tuberculosis occurs in September which is one to two/

two months later than the corresponding point for all causes of death.

In the other forms of tuberculosis this lag is much more pronounced, for death occurs most frequently in April and May and least frequently in November. When epidemics of influenza occur the slight lag in the seasonal trend of deaths from pulmonary tuberculosis is abolished, but the lag observable in the other forms of the disease is not affected.

In deaths from tuberculosis among young subjects below five years of age the same marked seasonal trend is observable as in the general mortality, but between the ages of 5 and 15 years the seasonal trend in deaths from tuberculosis is very much more marked than the tendency observable in the same age group for all causes of death. The difference is also present, though to a less marked degree, between 15 and 25 years of age, but thereafter diminishes.

In tuberculosis there is no difference in the seasonal trend of mortality as between the sexes.

Climatic conditions appear to be of importance in determining the extent of the seasonal variation in mortality in tuberculosis, but the influence of weather is less certain. It is probable that climate and perhaps weather also may modify the seasonal variation in the incidence of deaths from tuberculosis, but it should not be concluded that these are the only or even the most important factors concerned.

Addendum.- Since the above investigation was completed the Registrar General for Scotland has published similar information regarding a wide variety of conditions in the Supplement to his Seventy-eighth Annual Report, Part II (1936). The graphs in this report were constructed on the basis of the daily deaths per month per cent. of daily deaths per annum. As is the custom in considering vital statistics a natural decade (1921-1930) was selected for investigation. The present writer has pointed out, however, that the seasonal trend of mortality during this period was seriously disturbed by two midwinter epidemics of influenza, and that in consequence the monthly occurrence of deaths could not be regarded as the normal distribution. The above noted publication of the Registrar General does not therefore assist in the discussion of the present problem.

PART IV

DISCUSSION

Summary.- General Survey of the Present Investigation.

Basis of Discussion: A. Seasonal Variation in the Virulence of the Infecting Organism: B. Seasonal Variation in the Resistance of the Host.

Seasonal Variation in Normal Functions: (1) Body Weight (2) Body Temperature and Pulse Rate (3) Respirations (4) Metabolism (5) Mineral Content of the Body.

The Causes of Diminished Resistance During the Late Winter and Spring: (1) Nutritional Disturbance (2) Psychological Disturbance.

The Theory of Seasonal Variation in Disease.

Practical Implications of the Present Work.

General Survey of the Present Investigation.-

Before discussing seasonal variation in disease it is desirable to present a brief summary of the conclusions already gained in order to correlate the more important points. Certain features of this investigation in tuberculosis suggest a sequence of events in which the pathological process begins to exhibit increased activity in the winter and reaches its maturity in spring. Thus, it was noted that tuberculous glands began to increase in size more frequently in the month of January than at any other time. The/

The formation of pus in this type of lesion was most marked in the month of March. In pulmonary tuberculosis the corresponding change, the formation of sputum, was also observed to be most pronounced at that time.

Simultaneously with the softening process in local lesions during the spring, the systemic factor in tuberculous patients was observed to increase. This was indicated by the more frequent disturbance of the body temperature, and the decline in body weight. Lastly, death from tuberculosis was found to occur more frequently in March, April and May, than at other times of year.

Conversely, the morbid process appeared to be least active in the late summer and autumn. In tuberculosis of the lymphatic system glandular enlargement was least common in July and August. The softening process in the glands and in pulmonary lesions was relatively seldom seen in September, October and November. Systemically, febrile disturbances were noted to be least common during these months, and the body weight reacted most favourably. The mortality therefore was lowest from September to November.

Sex.- The study of the seasonal behaviour of body weight and more especially of seasonal disturbances in body temperature, in comparable groups of cases, led to the suggestion that in tuberculosis the female sex was possibly more susceptible to seasonal/

seasonal influences than the male sex. No support for this conception was derived from a statistical analysis of the incidence of fatal cases of tuberculosis in the principal towns of Scotland. But although the springtime disturbance of equilibrium between B.tuberculosis and the host may not be followed by any seasonal difference in the incidence of death as between the two sexes, it may nevertheless give rise to important variations during the clinical course of the disease. The evidence presented is not finally conclusive but it would appear probable that seasonal variation in tuberculosis is somewhat more pronounced in the female sex.

Climate and Meteorology.- Certain clinical observations recorded in different latitudes by various authors who studied seasonal changes in the body weight of tuberculous persons emphasise the importance of climatic influences in this respect. From a statistical study it was suggested that although climate and weather are not primarily responsible for seasonal variation in tuberculosis they may possibly cause the modifications which are observable in different countries.

Certain other results of this work, for example those relating to seasonal variation in selected diseases, or in certain age groups, do not require correlation with clinical findings or with the findings/

findings of other authors. The remainder of the statistical summary presented on pages 169 to 172 does not therefore call for further repetition.

BASIS OF DISCUSSION.- Seasonal variation in man, animal and plant is ultimately ascribable to the influence of the sun. It is the light and warmth of the sun which allows the earth to maintain life, and it is periodical changes in this light and warmth which result in the wide range of biological phenomena which may be described under the title of Seasonal Variation.

Since the effects of seasonal change are most obvious in the plant world, there is no apparent reason why the lowest forms of plant life, the micro-organisms, should not experience renewal of activity during the spring and also retrogression during the autumn, corresponding to the changes observable in the higher forms of vegetation. If this change occurs in micro-organisms which are pathogenic the seasonal occurrence of disease would result.

On the other hand, human resistance is not a constant factor. Fluctuations in the incidence of disease throughout the year may very possibly be due to alternating susceptibility and resistance caused by seasonal changes.

Seasonal variation in tuberculosis may therefore be associated with changes in the seed, or in the soil/

soil, or in both. These possibilities may be adopted as a basis for the discussion of the changes which have been described in this work.

A. Seasonal Variation in the Virulence of the Infecting Organism.- The investigator who attempts to discover if seasonal variation occurs in the biology of micro-organisms, finds himself confronted with certain difficulties despite the fact that such a change is decidedly possible on theoretical grounds. He cannot estimate bacterial virulence without animal experiment, and in employing animals he cannot state that any apparent increase in the toxicity of a certain strain of organism is not due to a diminution in the resistance of the experimental animal.

That seasonal change is an important factor in the laboratory animal house was first shown by Sudmer-sen and Glenny (1909) who stated that a much larger dose of diphtheria toxin was required to kill a guinea pig of given weight in the summer than in the winter. More recently Blake and Okell (1929) described a very marked variation in the mortality of mice which had been injected with dysentery (Shiga) toxin. The highest mortality among the mice occurred in February and the lowest in September.

The above two investigations indicate the type of difficulty which is encountered in studying seasonal change when a second variable quantity, a micro- /

micro-organism, is introduced into an experiment in place of a substance of constant toxicity. Nevertheless, Gaskell (1927) considered that in pneumococci a seasonal variation in virulence occurred which was so marked that it could not solely be due to the fluctuating resistance of the mice which he employed in his experiments. The data on which this author based his conclusions in relation to types 1 and 2 of the pneumococcus are recorded in Table 16.

Table 16.- Seasonal variation in pneumococcal virulence. The data in this table were derived from the analysis of a paper by Gaskell (1927).

Pneumococcus Type 1		Pneumococcus Type 2	
Date	Logarithm of reciprocal of M.L.D.	Date	Logarithm of reciprocal of M.L.D.
Summer, 1924	4 (below)	XI, 1924	3
II, 1925	4 (full)	II, 1925	4
VI, 1925	3	VII, 1925	3
I, 1926	4	XII, 1925	4
VI-VIII, 1926	3 (below)	II, 1926	3
I, 1927	4	VI, 1926	3
		III, 1927	4 (over)

From the above table it would appear that the variations noted are not sufficiently marked to warrant a definite conclusion as to seasonal variation in pneumococcal virulence, but whatever be the correct inference to draw from the published results it is interesting to recall the fact that pneumonia is a disease which exhibits very remarkable seasonal fluctuations.

Coburn and Pauli (1932) in America, and Blackburn and Others (1930) in this country, found that haemolytic streptococci may be isolated from the throat more frequently during the early months of the year than at other times. But this observation is not necessarily proof of increased microbic activity since the same findings might result from variations in human resistance.

In tuberculosis the same theoretical possibility requires examination. It is necessary to consider whether any of the seasonal phenomena which have been described in this work might be regarded as resulting more readily from an increase in the virulence of *B. tuberculosis* than from a diminution in the powers of resistance of the host.

From the clinical evidence available it is not possible to make such a deduction. Thus in local lesions, the early changes manifested in the swelling of tuberculous glands, and seen most frequently in January, might either be due to an increase in the virulence of the tubercle bacillus, or equally to a diminution the resistance of the patient. But the liquefaction of tuberculous lesions is thought to be due more to the proteolytic activity of certain cells rather than to the toxicity of the tubercle bacillus. This proteolytic action is held in check for a variable period of time but apparently it cannot be so readily restrained in March (and the spring generally) as at other times of year. Since it is improbable/

improbable that this restraining influence is the tubercle bacillus itself, it would appear that attention should be directed to the host rather than to the parasite in endeavouring to trace the causation of seasonal trends in the maturation of tuberculous lesions.

Similarly, the results which were obtained from a study of the systemic factor in tuberculosis furnished no conclusive evidence that the tubercle bacillus is a more noxious agent during the spring than at other times. On the contrary disturbance of body temperature may frequently be associated with the diminution of resistance, whilst the theory was actually advanced that the seasonal behaviour in the weight of tuberculous subjects was the expression of a normal tendency. The fact that the female sex was found to be more liable than the male sex to seasonal disturbances in body temperature (and to a less extent in body weight), would seem to indicate that if the tubercle bacillus does undergo a seasonal change in virulence, it is not the only factor concerned, but that some variation must take place in the host also.

It might be anticipated that the seasonal variation which was noted in the tuberculin reaction might provide more definite evidence on this problem. But it would appear that the accelerated antigen-antibody reaction which occurred during the month of April/

April might either be due to an increase in the antigenic power of *B. tuberculosis* at that time, or to an increase in the power of the body cells to produce antibodies in response to the stimulus from the bacillus.

On clinical grounds, therefore, it is not possible to suggest that the tubercle bacillus varies in virulence at different times of year. But the interpretation of the results emerging from the statistical portion of this work rather tends to support such a contention.

Thus, in considering the seasonal variation in the mortality from different diseases, it appears that the theory of variation in microbic virulence is not only tenable but essential. The extreme variation observable in the incidence of deaths from the acute infections of the respiratory system; the less pronounced trend in the mortality from chronic organismal diseases such as tuberculosis and syphilis; the slight seasonal variation in the mortality from appendicitis; and the absence of such change in the mortality from malignant disease, are all facts which emphasise the infective nature of the types of sickness in which seasonal variation is most apparent. It does not appear probable that such wide diversity of seasonal change in mortality could be solely due to fluctuations in the resistance of the human subject.

But there are other types of variation than/

than those noted above. Whilst deaths from most infective diseases were particularly frequent in March, there were certain notable exceptions. Thus in children under two years of age fatal cases of Diarrhoea and Enteritis were most frequent in August and September. In older subjects Enteric Fever, although much less in evidence than in former years, is still said to be most common about the same time. It seems probable, therefore, that conditions which are most favourable for one group of micro-organisms may be entirely unfavourable to another group.

In tuberculosis also the seasonal trend in mortality was unlike that of most other diseases, chiefly on account of the fact that there was a lag in the increased incidence of deaths during the spring. This lag might at first sight be due to the fact that tuberculosis is a chronic disease, but two observations tend to discount this explanation. Firstly, in syphilis, also a chronic disease, no such lag was noted. Secondly, the lag in the seasonal trend of deaths from tuberculosis was most pronounced in the most acute form of the disease, namely meningitis. The inference is, therefore, that the lag in the seasonal incidence of deaths from tuberculosis is not due to the chronicity of the disease, but rather to the fact that tuberculosis has a peculiar seasonal trend of its own. The explanation of this finding is more likely to be noted in seasonal change in the causal organism than/

than in the host.

The theory of seasonal variation in the life of *B. tuberculosis* gains further support from the following consideration. The natural seasonal variation in mortality (i.e. that occurring from all causes of death including tuberculosis) was found to be much less pronounced between the ages of 5 and 15 years than at any other time of life. And yet in this age group the seasonal trend in the deaths from tuberculosis alone was very marked indeed. Now, if fluctuations in the resistance of the individual were responsible for seasonal changes in mortality, it would be difficult to understand why the variation for the collected diseases should be so slight whilst that for tuberculosis should be so pronounced.

The available evidence on seasonal variation in micro-organisms may be summarised as follows. On clinical grounds it is not possible to assert that any of the seasonal changes observed in the human subject were more probably due to a seasonal increase in the virulence of the invading organism than to the reverse change in the resistance of the host. On the contrary, certain findings seem to point more definitely to the latter possibility. But on statistical grounds it may be stated that certain phenomena were observed which may only be explained by seasonal variation in the biology of the micro-organisms concerned.

Apparently therefore both factors are operative in the causation of seasonal variation in disease, and in order to estimate the relative importance of each, attention must now be devoted more particularly to seasonal variation in man.

B. Seasonal Variation in the Resistance of the Host.- Certain of the changes described above seem to point to the existence of seasonal variation in man rather than in micro-organism. In particular the seasonal change in the body weight in tuberculosis was considered to be more or less a normal change. Further, the marked discrepancy in the extent to which the body temperature in tuberculous subjects of different sexes was disturbed in the spring, also suggested the occurrence of seasonal fluctuations in the patients themselves.

It is necessary, therefore, to ascertain whether any comparable changes which might possibly be associated with diminished resistance in the spring of the year, have been described by other authors as occurring in normal people. Seasonal trends in body function are beginning to form the subject of inquiry and there is a variety of information to be considered. Generally speaking the available data were found to be based on very restricted clinical material, and if observations made on three or four subjects are repeatedly referred to in this discussion, it is/

is because more extensive investigations do not appear to have been published.

The present position regarding physiological seasonal variation may be summarised as follows.

(1) Body Weight.— Seasonal change in body weight, both in normal and tuberculous subjects, has already received detailed consideration in this work. In normal children there is a period of slow increase in weight during the spring and a more rapid gain at all other times of year. The only corresponding investigation in normal adults which has been available for reference is that of Griffiths and others (1928) and is only based on five subjects comprising three men and two women. The authors stated that the weight of these persons increased during the winter and decreased during the spring and summer. As has been stated (page 95) the average difference between maximum and minimum recordings, translated into imperial weights, amounted to $2\frac{1}{2}$ pounds.

(2) Body Temperature and Pulse Rate.— According to Griffiths and others (1928) the body temperature recorded under resting conditions presents a seasonal variation, the lowest readings being most commonly observed in the spring. The same authors (1929) stated that the pulse rate while at rest was highest in February and lowest in August. The latter observation they regarded as one of the most definite emerging from their series of observations on this subject.

A parallel observation to that noted above on the body temperature was made by Monro (1933) who found that the proportion of cases admitted to certain wards of Edinburgh Royal Infirmary which exhibited subnormal temperatures was greater in March than at other times of year. The present writer, in his examination of the body temperature in tuberculosis, was unable to explore the possibility of seasonal variation in subnormal temperatures since it is not the custom in sanatorium work to employ thermometers registering lower than 96°F. But it will be recalled that the body temperature was more unstable during the spring than at other times of year.

(3) Respiratory Function.— Griffiths and others (1929) have noted that the oxygen content of the expired air is lowest in spring and highest in the late summer and autumn, but they were unable to observe seasonal variation in the respiratory rate. Lindhardt however, (quoted by Madsen 1930) not only found that the carbon-di-oxide tension was maximal in January, February and March, and minimal from June to September but also stated that a corresponding variation of the respiratory rate occurred. It is interesting to note that independently of the above observations Isachsen (quoted by Madsen 1930) discovered that the haemoglobin of the blood as estimated by Gower's method was lowest in the months of December, January and February, and highest from June to September.

The above observations were all based on small numbers of cases, 5 by Griffiths, 4 by Lindhardt and 13 by Isachsen, but since all were closely in agreement, except for the difference regarding respiratory rate, a fair measure of reliability may be placed on the conclusion that there is a tendency to diminished respiratory efficiency during the spring of the year.

(4) Basal Metabolic Rate.— The evidence regarding seasonal change in metabolism is not clear. Gustafson and Benedict (1928) in a study based on 20 female subjects found that the basal metabolic rate was low in winter, but high in spring and summer. Hitchcock and Wardwell (1929-1930) stated that metabolism was lowest in winter and spring, but highest in summer and autumn. These two observations therefore differ in relation to the spring, but since the latter inquiry was based on four subjects of whom only two were followed for a complete year, greater reliance attaches to the former observation.

More conflicting data are to be found in the published work of Pucher and others (1934) on seasonal variation in certain urinary constituents. The experimental data were derived from the examination of four cases under basal conditions of diet and rest. The results indicated that the total nitrogen excretion was greatest in winter and least in the early autumn. The partition products of nitrogen (urea, creatine, creatinine, uric acid and amino-acids) all/

all revealed similar but less well defined changes. These observations would seem to point to increased metabolism during the winter.

It is not possible to draw any conclusion from the evidence at hand as to the occurrence of a seasonal variation in the basal metabolic rate.

(5) Mineral Content of the Body.- Three minerals namely phosphorus, calcium and iodine have formed the subject of inquiries relating to seasonal change.

(a) Phosphorus.- There can be little doubt that the amount of phosphorus in the human body varies at different times of year. Hess and Lundagen (1922) have demonstrated the fact that such variation is most pronounced in infants. In 60 cases the minimum values of phosphates in the blood (3.75 mgm. per cent.) were noted in March, whilst the maximum values (4.3 mgm. per cent.) were observed in the summer. They further called attention to the interesting fact that the better the quality of the milk the higher was the absolute recording of phosphates in the blood, but that the seasonal fluctuation was always the same. In 10 older children the seasonal trend was slightly less pronounced, whilst in a series of normal adults the absolute values were much lower and much more stable. The changes outlined above were similar to the observations noted by Pucher and others (1934).

(b) Calcium.- Hoyle (1928) has stated that seasonal change occurs in the serum calcium of rabbits, but in/

in human beings this opinion is not held. Pucher (1934) was unable to determine any such change. while Hess and Lundagen (1922) only found it to occur to an inconsiderable extent in young infants.

(c) Iodine.— A comprehensive review of the part played by iodine in human nutrition has been compiled by Orr and Leitch (1929). In studying the source of this mineral they found that the amount of iodine in Scottish pastures steadily increased during the autumn. They correlated this information with the findings of Martin (1912-1913) who demonstrated a definite seasonal variation in the amount of iodine in the thyroid glands of ruminants, the maximum occurring in autumn and the minimum in spring. In America Seider and Fenger (1912) found even more marked results, and stated that in healthy cattle, sheep and pigs three times as much iodine was found in the thyroid glands during the period from June to November as compared with the period December to May.

Orr and Leitch also found that there was a seasonal variation in the iodine content of human blood. Thus the average amount of iodine in the blood of 16 healthy people during the spring was 6.0 γ per 100 cc. whilst the average figure for 28 subjects during the autumn was 8.4 γ per 100 cc. On the whole these results were not quite so high as the later figures of Schittenhelm and Eisler (1932) who reported on the examination of the blood in respect of iodine in 300/

300 cases. The average readings given by these authors were 8 to 12 γ per 100 cc. from March to October, but during the winter and early spring these figures were 7 to 9 γ per 100 cc.

It must be concluded from an examination of the evidence that man (and animal) are subject to seasonal variation which may be manifested in various ways. It would seem that there is a period between January and May, and particularly from March to April, when nutrition, using that term in its widest sense, is interfered with. It is now necessary to ascertain what external factors may lead to the production of these changes, and whether they might be associated with seasonal diminution in the resistance to disease.

The Causes of Diminished Resistance During the Late Winter and Spring

As has been stated above all seasonal influences are ascribable to the sun. But the mode of action of the sun in promoting the observed changes is not clear. In particular it is strange that whilst the spring brings renewed vigour to various forms of life, it should apparently bring diminished resistance to man. It is probable that the causes of this diminution in human resistance occurring in spring may be classified firstly as nutritional, and secondly as/

as psychological. Each of these will require consideration.

A. Seasonal Variation in Nutrition.- Seasonal deficiency in an important part of the diet would almost certainly cause nutritional disturbances which might affect bodily resistance to disease. In this country, in times of peace, there is no such deficiency in respect of proteins, carbohydrates and fats which form the gross essentials of the national dietary. But, in view of the changes which have been noted above in relation to phosphorus and iodine, there is reason to believe that the more subtle elements of the diet, the minerals, and by inference the vitamins also since they are largely interdependent, undergo a seasonal variation.

It is desirable, therefore, to examine the vitamin content of the diet at different times of year, and to ascertain firstly, if seasonal variation does in fact occur, and secondly, whether it might possibly be associated with seasonal variation in the resistance to disease. In connection with the latter possibility it is important to note the views of Hopkins (1935). This author stated that "It cannot be made too clear that a relative deficiency in any one of these (vitamins) may be the cause of subnormal health, and if long continued in infancy or youth, may do permanent harm." In the light of this statement/

statement further examination of the vitamin content of the diet may be made.

Vitamin A.- The richest sources of vitamin A in the normal diet are vegetables, milk, and certain animal tissues, notably the liver. It is probable that the last of these need not be regarded as an important source of the vitamin except in a small proportion of individuals.

But as far as the majority of the population are concerned the supply of vitamin A from vegetables must be very deficient during the late winter and spring, since fresh green foods are difficult to obtain and are also prohibitive in price.

The amount of vitamin A in milk also varies according to the season of the year. Thus Chick and Roscoe (1926) found that the vitamin content in the milk of a cow fed on summer diet (fresh green food) was much greater than that of the same cow fed on winter food (cereals and roots). It would therefore appear probable that during the early months of the year there is a relative deficiency of vitamin A in the human diet.

Further evidence in support of this contention is to be found in the seasonal occurrence of Keratomalacia. Madsen (1930) observed that the maximum incidence of this disease was recorded in the late spring, and a minimum incidence in the late summer and autumn.

But apart from the intimate relationship of vitamin A to eye disease, the wider importance of this factor in general nutrition must be emphasised. The views of Hopkins regarding the importance of all vitamins have been noted above. But E. Mellanby (1934) in summarising the present state of knowledge of vitamin A has concluded that "When the vitamin A reserves are not depleted but when nevertheless there is reason to believe that some deficiency may exist, human beings are more susceptible to certain types of infection, and their resistance to these types of infection may be raised by vitamin feeding." The types of infection referred to by this author were xerophthalmia, various catarrhs especially of the respiratory system, pneumonia and tuberculosis.

In discussing the relationship of these diseases to vitamin A, Mellanby referred to the important monograph by Orr and Gilks (1931) on the incidence of certain types of sickness among two neighbouring African tribes, the Akikuyu and the Masai. Bronchitis and pneumonia among the former, who are a cereal eating people accounted for 31 per cent. of all cases of illness, and pulmonary tuberculosis for 6 per cent. Among the Masai, however, whose diet consists largely of meat, milk and raw blood, the corresponding figures were 4 per cent. and 1 per cent. These findings furnish strong evidence regarding the importance of vitamin A in the prevention of tuberculosis.

Closer inspection of this report reveals another difference between the diets of these two tribes which seems to have attracted less attention from commentators. The customs of the Akikuyu result in a diet containing little sodium, little calcium, and an excess of phosphorus, whilst those of the Masai lead to a diet in which the mineral constituents are more suitably balanced. The importance of vitamin A in relation to the diseases mentioned is not lessened by this observation since the relationship between vitamin and mineral metabolism is much closer than was at one time thought.

The mechanism by which the absence of vitamin A causes diminished resistance was studied by Werkman (1923). He found that rabbits fed on test diets produced haemolysins, precipitins, agglutinins and bacteriolysins as abundantly as those on a normal diet. But the phagocytic activity of the leucocytes of the rabbits on the test diets was considerably less than that observed in rabbits on normal diets. The interpretation of this investigation, however, is complicated by the fact that the experimental diets employed were not only deficient in vitamin A but also in vitamin B.

The relationship of vitamin A to seasonal variation in disease particularly tuberculosis, may be summarised as follows. A relative deficiency in the supply of vitamin A results in subnormal health, and/

and predisposes to certain diseases including tuberculosis. A deficiency in this vitamin occurs in the diet of most individuals during the late winter and spring. Therefore the increase in the activity of the tuberculous process at that time may be associated with an insufficiency of vitamin A. The nature of this relationship is uncertain but, subject to further confirmation, may possibly lie in a diminution of the phagocytic power of the leucocytes.

The Vitamin B Complex and Vitamin C.- The accessory food factors known as the vitamin B complex and vitamin C may be considered together since a detailed commentary on their relationship to seasonal variation in man is not at present possible apart from the incidence of those diseases with which they are specially associated.

For the majority of the population of this country the amounts of vitamins B and C available in the dietary vary widely at different seasons. Since they are not capable of being stored in the body for any length of time, a relative deficiency is probable during the late winter and spring. This deficiency is possibly more pronounced in relation to vitamin C since its distribution in food stuffs is practically confined to fresh vegetables and fruits. Nothing is known regarding the seasonal variation of vitamin C in milk though on theoretical grounds such a variation is decidedly probable. The vitamin B complex/

complex, however, varies in milk in much the same way as vitamin A was observed to vary. Hunt and Krauss (1931) found that the milk from cows on pasture contained much more vitamin G (B₂) than did the milk from cows on "dry feed". Smaller amounts of vitamin B (B₁) were found to be present in milk and the seasonal change, though successfully demonstrated, was less marked than in the case of vitamin G (B₂). Probably the only common source of the vitamin B complex which does not vary with the time of year is brown bread, and it is doubtful whether brown bread is consumed in sufficient quantities to prevent the occurrence of seasonal variation in the supply of this vitamin.

Since both vitamins B and C appear to be deficient in amount in the spring of the year it is possible that a state of subnormal health may be unusually prevalent about that time, predisposing to various diseases including tuberculosis. In the absence of further clinical or experimental evidence this hypothesis cannot be regarded as reliable.

Vitamin D.— The dietetic sources of vitamin D are almost entirely confined to liver and yolk of egg in which the vitamin is abundant, and to milk in which it is relatively poor. Almost all human beings however derive the greater part of their supply of vitamin D from insolation, through the interaction of skin and ultra-violet light. This being so there is a pronounced seasonal variation in the natural/

natural synthesis of vitamin D. Tisdall and Brown (1931) have stated that in Toronto the power of the ultra-violet light of the sun to prevent rickets in experimental animals increases rapidly after the mid-day sun reaches an altitude of 35° above the horizon. (This occurs about February 15 in Toronto but earlier in lower latitudes and later in higher latitudes.)

To what extent this variation is neutralised by the power of the body tissues to store the vitamin is problematical, but the manifestations of gross deficiency undoubtedly present a seasonal incidence. Thus, in England the incidence of acute rickets is at a maximum in March and April and at a minimum from September to December (Stallybrass, 1928). In Vienna Chick and others (1923) noted that infants fed on the same diet developed rickets in winter but not in summer. But apart from these marked cases it is quite possible that a less pronounced lack of the vitamin, which must be extremely common during the winter, may also cause seasonal changes in the direction of poor health and failing resistance.

In connection with this possibility it is interesting to note that certain aspects of normal mineral metabolism are closely related to the presence of vitamin D, and in particular the body is unable to utilise calcium unless an adequate supply of this vitamin be present. It is therefore possible that despite the absence of seasonal variation in the amount of/

of serum calcium in the animal body, unsatisfactory utilisation of this mineral during the late winter and spring may nevertheless occur due to a relative deficiency in the supply of vitamin D.

Experimental evidence supports this theory.

Grant and others (1927) have shown that rats which are normally resistant to B.tuberculosis even in doses of 1 mgm. can readily be infected if their resistance is lowered by a diet deficient in vitamin D and calcium, They have further shown that during the winter when animals are more dependent on diet than on light for their supply of vitamin D, the susceptibility both to tuberculosis and rickets is increased, and that by the time spring arrives the severity of both diseases attains its maximum.

The indication is that tuberculosis is not only predisposed to by subnormal health due to a diminution in the supply of vitamin D, but that the healing of existing lesions may perhaps be interfered with more directly by the inability of the body to utilise the available supply of calcium.

Summary of the Possible Part Played by Vitamins in the Production of Seasonal Variation in Disease, and especially in Tuberculosis.- The possible role of the vitamins in relation to seasonal variation in disease may be summarised as follows. A partial deficiency of any of the accessory food factors may cause subnormal health, and predispose to various diseases. During/

During the late winter and spring a relative deficiency occurs in all vitamins, and a general lowering of resistance probably ensues. As far as the seasonal susceptibility to tuberculosis is concerned it seems probable that the periodical deficiency of vitamins A and D is more important than the lack of vitamins B and C.

B. Seasonal Psychological Reactions.- The writer is not sufficiently versed in the methods of psychological research to formulate evidence acceptable to the expert psychiatrist in order to ascertain if psychological disturbances of a seasonal character occur, and give rise to a relative diminution in the resistance to disease.

And yet the possibility may not be justly omitted from consideration especially in relation to tuberculosis. Many normal people experience periods of mental depression towards the end of winter, and during the early spring, and find their daily occupation unusually burdensome. Presumably there are many individuals in whom this type of mental state does not intrude itself upon the open consciousness. But in tuberculous patients the inward repugnance to the winter and early spring is a common and real experience, and one with which all sanatorium physicians are familiar. They find that mental depression is much more common during the period from December to/

to March than at any other time, and that it is largely banished by the returning sunshine of April and May.

It is difficult to state whether this type of mental reaction is the cause or the effect of seasonal diminution in resistance. Possibly a vicious cycle is established in which diminished nutrition becomes associated with mental depression, which in turn further lowers physical resistance. The writer however considers that the psychological factors cannot be left out of account in classifying possible agents in the causation of seasonal incidence in disease, but that its mode of influence requires more expert study.

The Theory of Seasonal Variation in Disease

As far as can be ascertained from the information which has been available seasonal variation in disease must be explained as follows.

Primary Changes in the Human Being.- The first essential is apparently seasonal change in the "soil". There is a variety of cumulative evidence which, although no single part is thoroughly convincing, would seem to indicate that there is seasonal variation in the physiology of healthy people. This variation is said to be observable in body weight, respiratory efficiency, body temperature and pulse rate, and possibly in other directions. These observations require to be extended and confirmed, but the inference is that/

that at the end of winter and during the early spring nutrition (using the term in its widest sense) is interfered with.

The observations which justify this deduction arise in part from seasonal deficiencies in the vitamins, especially vitamins A and D, together with the associated disturbance of mineral metabolism; in part from psychological disturbances; and in part perhaps from other agencies as yet unknown.

The precise nature of the change in the human subject is obscure, as it must be until the mechanism of human resistance is clearly understood. But it is evident that the age and sex of the subject bear some relationship to springtime diminution in resistance. Young children become more susceptible to illness during the late winter and spring than do adults. In tuberculosis older children also exhibit this phenomenon to an unusually marked degree, whilst female patients offer more ready evidence of seasonal change than male patients.

Secondary Factors.- With the above noted changes in the "soil", the stage is set for seasonal variation in disease, and the actual type of fluctuation which results now depends on certain other factors, notably on the "seed".

In general it may be stated that the infective diseases are more prone to exhibit seasonal change/

change than the non-infective diseases. Further, certain bacteria seem to be much more variable than others in their seasonal relationships. Some find the optimum conditions for growth in the late winter and spring, and others in the late summer and early autumn. Some are associated with very violent seasonal reactions and others with relatively mild seasonal trends.

Climate and weather must rank last among the factors which are known to be related to seasonal change. In tuberculosis (though not in all infective diseases) climate is the more important, whilst weather seems to be of little consequence.

Practical Implications of the Present Work

Hitherto this discussion has been concerned with evidence relating to the theoretical aspect of seasonal variation in disease. But in conclusion certain practical implications as regards tuberculosis are worthy of attention. These may be conveniently examined under the headings of Diagnosis, Prognosis and Treatment.

Diagnosis.- From the data furnished in Parts I to III of this work it might be supposed that tuberculosis should be more frequently diagnosed in the late winter and spring than at other times of year. If every physician notified his cases of tuberculosis/

tuberculosis "Forthwith on becoming aware" of the true nature of the illness, a definite seasonal trend in the incidence of new cases might occur. But the irregularity with which returns are made renders the seasonal investigation of new notifications a procedure of doubtful value.

Glandular tuberculosis would seem to occur most frequently in January and February. But it must not be supposed that pulmonary tuberculosis is readily diagnosed in the stage at which the pathological change in the lung corresponds to that of glandular enlargement. For the most part pulmonary tuberculosis is still diagnosed in the stage of softening of lesions. This occurs most frequently in March and April, and at that time physicians should be more suspicious than ever in doubtful cases.

Prognosis.- In assessing the prognosis of patients suffering from tuberculosis it is a common practice to base an opinion on the response to the first two months of treatment. The majority of patients in whom the ultimate result is satisfactory show signs of commencing improvement within this period of time. But it is important to take into consideration the season of the year. The prognosis in a patient who loses ground in the spring is not necessarily poor since the spring is a danger period in all cases. But the prognosis in a patient who loses ground in the autumn should be regarded more seriously, since that/

that is the time when the majority of tuberculous subjects may be expected to improve.

The prognostic significance of certain signs arising in the course of tuberculosis should be interpreted in the same way. For instance, a steady loss of weight during the months of February, March and April need not be regarded with disquiet unless it is very pronounced. But failure to gain weight in the autumn should always cause suspicion that all is not well.

It is not justifiable, however, to ignore frequent, slight febrile disturbances in February, March and April on the ground that they constitute part of a seasonal reaction. It is permissible to disregard a moderate diminution in weight during the spring because normal people would appear to exhibit this phenomenon. But it cannot be stated that febrile disturbances, however slight, are the result of seasonal change. On the contrary, they must always be regarded as indications of active disease and treated accordingly.

Treatment.- Since the resistance of the individual is low during the late winter and spring, the treatment of tuberculosis demands especial care at that time. The diet should receive particular attention in order to ensure an adequate supply of vitamins A and D. As has been noted the ordinary food stuffs probably contain inadequate supplies of these/

these vitamins at the very period during which they are most needed, and therefore the deficiency must be made good by the exhibition of the oils of cod or halibut liver. This should be commenced about December. The practice of supplying excess of vitamins by special methods during the summer and autumn is probably no more necessary for the average case of tuberculosis than the provision of artificial light therapy during the season of natural sunshine. Wherever possible special dietetic measures should be reserved for the danger period.

General ultra-violet radiation should be employed in all cases in which there is no definite contraindication, from December to February. It is during these months that the storage reservoirs of vitamin D tend to become depleted and the natural ultra-violet radiation from the sun is deficient. In sanatorium work, however, the extensive employment of ultra-violet light is not so essential as in dispensary practice for two reasons. Firstly, cases attending dispensaries as out-patients are more likely to suffer from diets deficient in vitamin D than patients resident in sanatoria. Secondly, the period of inadequate sunlight is much longer in the areas served by dispensaries, mostly industrial districts and large towns, than that experienced by the sanatoria of the same district. This is of course the result of atmospheric pollution by smoke. In dispensary/

dispensary work therefore every suitable case should be afforded the benefits of ultra-violet light throughout the winter and spring, and children should be given priority in this respect since they are by far the most susceptible to seasonal change in tuberculosis. Fortunately the importance of ultra-violet light in this connection is being appreciated by local authorities, and the establishment of suitable clinics is proceeding apace.

Other special measures in treatment require consideration. Thus the tendency of tuberculous lesions to activate during the spring necessitates the strictest control of reactions to any therapeutic procedure. The indications for the curtailing of exercise, or for the reduction of dosage in tuberculin or gold treatment must be more stringent than ever. The artificial pneumothorax demands particularly careful management. The collapse should be commenced, wherever possible, before the beginning of the danger period, and in order to avoid reactions during this period refills should be small and frequent.

Finally, the discharge of patients between February and April requires careful attention. Unless a lesion be firmly cicatrised it is advisable to maintain sanatorium treatment until after the danger period. Ideally the patient who is not fit for discharge in January should be advised to remain under observation till the end of April. This procedure/

procedure is however complicated by the increasing number of applications for admission commonly received during the spring, but wherever possible patients should be encouraged to remain under treatment till the spring is passed.

The above investigation has not resulted in a complete explanation of seasonal variation in disease. The theory formulated fits the known facts but certain important gaps remain to be filled. The first concerns seasonal variation in micro-biology. Direct evidence on this question is lacking, and the indirect evidence is inconclusive. Secondly, more reliable knowledge is required regarding seasonal changes in normal people, for variations brought to light in relation to abnormal conditions are found to be somewhat inadequate in discussing a biological problem. Lastly, before seasonal variation can be comprehended the mechanism of resistance must be explained. When, and only when, the above problems are solved seasonal variation in man and animal will be understood. The present investigation should be regarded as a contribution to this interesting problem.

SUMMARY

Tuberculosis is a disease which exhibits well defined seasonal changes. The phenomena described above fall conveniently into three groups, namely, I Clinical Observations on Local Lesions: II Clinical Observations on Systemic Manifestations: and III Seasonal Variation in Mortality. The conclusions gained from these investigations may be summarised as follows.

I Seasonal Variation in Local Lesions.- A. Glandular Tuberculosis.-

(1) The appearance of glandular swelling in tuberculosis of the lymphatic system occurs most commonly in the months of January and February, and least commonly in August and September.

(2) The formation of pus in these lesions is observable most frequently in March and April, and least frequently in August, September and October.

B. Pulmonary Tuberculosis.- (1) Sputum is expectorated in greater quantities during March and April than at any other time of year, and conversely, is least abundant in June and July.

(2) There is no seasonal tendency in the incidence of pulmonary haemorrhage.

II Seasonal Variation in the Systemic Factor.-

A. Body Temperature.- The body temperature in tuberculosis is very unstable, but the instability is especially marked in the months of February, March and April. This statement is true even of mild cases including adults of both sexes and children, but applies particularly to adult female patients.

B. The Pulse Rate.- No seasonal variation is observable in the pulse rate of tuberculous patients.

C. Body Weight.- A well defined seasonal change occurs in the weight of tuberculous patients. A decline is noticeable during February, March and April, and is followed by an increase during the late autumn and early winter. In children this change is one of slow growth in the early part of the year, and rapid growth in the later part of the year.* It is suggested, however, that these variations are the expression (possibly exaggerated) of a normal tendency.

D. The Tuberculin Reaction.- The response to tuberculin is probably more rapid during the spring than at other times of year.

III Seasonal Variation in Mortality/

* This statement applies only to growth in weight and not to growth in height.

III Seasonal Variation in Mortality: A. Tuberculosis.

(1) Tuberculosis (All Forms).- A seasonal fluctuation is observable in the mortality from tuberculosis (all forms) in which the maximum proportion of deaths occurs in March, April and May whilst the minimum proportion is recorded from August to November. The extent of this seasonal change is represented by a variation of approximately 20 per cent. above and below the average number of deaths per month.

(2) Pulmonary Tuberculosis.- The seasonal change in the mortality from pulmonary tuberculosis resembles that from all forms of the disease except that the maximum and minimum points are recorded somewhat earlier in the year.

(3) Meningeal Tuberculosis.- In meningeal tuberculosis the seasonal variation in mortality is very much more pronounced, amounting to a fluctuation of approximately 30 per cent. above and below the average number of deaths per month. The maximum and minimum points occur later in the year, namely in May and November respectively.

(4) Other Forms of Tuberculosis.- The variation in mortality observable in the remaining manifestations of tuberculosis, resembles that of pulmonary tuberculosis in its extent, but that of meningeal tuberculosis in time.

(5) Sex.- No evidence exists which supports the view that the female sex is more susceptible than the male sex to seasonal variation in the mortality from tuberculosis, despite the fact that certain clinical features in the course of the disease supported such a contention.

B. The General Mortality, and Certain Selected Diseases.-

(1) General Mortality.- The maximum mortality from all causes occurs in March, and the minimum in September. The seasonal reaction is similar to that observed in tuberculosis in its excursion above and below the average number of deaths per month though the maximum and minimum points occur somewhat earlier in the year.

(2) Influenza (Endemic), Pneumonia, and the Principal Respiratory Diseases (not tuberculous).- The seasonal trend in the mortality from these diseases is very pronounced indeed, the highest and lowest returns being made in March and September.

(3) Appendicitis and Syphilis.- The seasonal variation in the mortality from appendicitis and syphilis is relative/slight.

(4) Cancer.- There is no seasonal variation in the mortality from malignant disease.

C. The Relationship of Age to Seasonal Variation in Mortality.- Young children (below five years of age) are very much more susceptible to seasonal/

seasonal variation in disease than older subjects. This is true of the collected causes of death, but in tuberculosis the susceptible age extends to 15 years before the seasonal variation in mortality commences to diminish.

D. The Relationship of Climate and Weather to Seasonal Variation in Tuberculosis.- Climate is undoubtedly an important factor in the determination of seasonal variation in tuberculosis. This may be observed in the available evidence on mortality in different countries, and in clinical observations recorded in different latitudes. It is probable that less significance attaches to weather in the causation of seasonal trends in tuberculosis however important it may be in acute respiratory infections.

The Causes of Seasonal Variation in Disease.-

The causes of seasonal variation in tuberculosis, and in almost all diseases are probably very complex. But they may be stated to be associated with (a) changes in the human subject, and (b) changes in the micro-organism. The evidence available from this work and from other sources is discussed from this point of view. It would appear that changes in the "soil" are the more important, but that changes in the "seed" govern to some extent the nature of the variation which results.

Practical Implications.- Consideration is given to the importance of seasonal fluctuations in the treatment of tuberculosis
